# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203188Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA Serial Number:** | 203188/SN000 |
| **Drug Name:** | Kalydeco (Ivacaftor or VX-770) 150 mg tablets |
| **Indication(s):** | Cystic Fibrosis in patients > 6 years of age with a G551D mutation in the CFTR gene |
| **Applicant:** | Vertex Pharmaceuticals, Inc. |
| **Date(s):** | Stamp: 10-18-2011; PDUFA: April 18, 2012 |
| **Review Priority:** | Priority |
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# 1 EXECUTIVE SUMMARY

Vertex Pharmaceuticals, Inc. has submitted two Phase 3 studies (102 & 103) and one Phase 2 study (104) in subjects with Cystic Fibrosis. Subjects in trials 102 &103 had the G551D mutation while those in trial 104 were homozygous for the F508del mutation. For the G551D subjects in trials 102 & 103, statistically significant results against placebo were found for the primary endpoint (absolute change in percent predicted FEV1 through week 24) and key secondary endpoints (CFQ-R score through weeks 24 and 48, change in sweat chloride concentration through weeks 24 and 48, time to first pulmonary exacerbation through weeks 24 and 48, and change in weight at weeks 24 and 48). P-values were consistently less than .001. Both trials indicated that the median change from baseline in the primary endpoint was approximately 10 % in the Ivacaftor group and zero in the placebo group through 24 and 48 weeks. Trial 104 was unsuccessful in showing efficacy in subjects with the F508del mutation. The average change from baseline in percent predicted $FEV_1$ was only (b) (4) through week 16.

# 2 INTRODUCTION

## 2.1 Overview

Vertex Pharmaceuticals, Inc. has submitted the results from two Phase 3 studies (102 & 103 Part B) and one Phase 2 study (104) study to support the regulatory approval of Ivacaftor (or VX-770) 150 mg tablet for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the CF transmembrane conductance regulator (*CFTR*) gene. The treatment is administrated orally every 12 hours (q12 h). The proposed trade name is Kalydeco. Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and at present, there is no cure. Kalydeco is not currently marketed for any indication in the United States or other countries.

The Phase 3 studies, referred to as 102 and 103b, are randomized, double blind, placebo-controlled studies to assess the efficacy and safety of 24 weeks of treatment with Ivacaftor 150 mg q12h in subjects age 12 years and older (Study 102) and 6 to 11 years (Study 103b), see Figure 1. Placebo-controlled treatment was continued through 48 weeks to further assess safety and to confirm the durability of response. Subjects who completed 48 weeks of treatment were eligible to enroll in a long-term open-label study (Study 105). The same primary endpoint - the absolute change from baseline in percent predicted $FEV_1$ through Week 24 - was selected for the placebo-controlled Phase 3 studies. For each of the two studies, absolute change from baseline in sweat chloride, absolute change from baseline in CFQ-R (respiratory health domain), time to pulmonary exacerbation (Study 102 only), and change from baseline in weight were pre-specified as key secondary endpoints. A sequential procedure for testing the primary and secondary endpoints was pre-specified to control the overall Type 1 error rate due to multiple key secondary endpoints. Study 102 was designed to enroll a minimum of 80 subjects to provide at least 80% power to detect a treatment effect of 4.5 percentage points in absolute change in percent predicted $FEV_1$ (refer to Appendix 1 for power calculation) and Study 103b was designed to enroll a minimum of 30 subjects.



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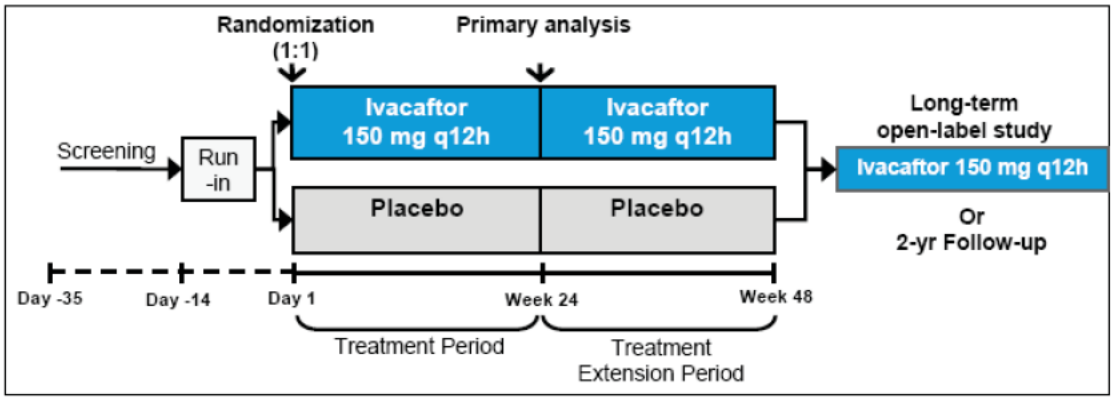
Figure 1: Schematic of Phase 3 Studies of Ivacaftor




Note: Schematic shown represents Studies 102 and 103 Part B. The long-term open-label study is Study 105.
Source: Module 2.5 Clinical Overview, page 14

Study 104 was a phase 2, double-blind, placebo-controlled study of Ivacaftor 150 mg q12h in subjects 12 or older who were homozygous for the F508-CFTR mutation. It was designed with Part A to be 16 weeks with an open label extension (Part B) up to week 112. Part B enrolled only subjects who had 'responded' in Part A as defined by 1) an increase of at least (b) (4) from baseline in % predicted $FEV_1$ and 2) a decrease in sweat chloride concentration of at least (b) (4) at both the Day 15 and Week 8 visits. Only Part A results are given in this document, referred to as 104a. Statistical methods were the same as in Studies 102 and 103.

Communication with the sponsor regarding these studies is documented under IND 74633. Pertinent parts of the statistical portion of those communications are summarized herein. The Division reviewed the statistical analysis plans (SAP) for Studies 102 and 104a under serial numbers 109 and 122 (dated May 17, 2010 and September 7, 2010, respectively), and for Study 103 under serial number 122. Comments on their SAPs were provided to the sponsor. The statistical comments pertain mostly to the handling of missing data and multiplicity. The Division informally agreed with the sponsor's proposal for the primary efficacy endpoint. The Division also informally agreed to the statistical analysis plan for the primary efficacy endpoint, their planned approach to handle missing data and the method to control the type I error for the analyses of the primary and key secondary endpoints (Division Fax letter dated December 2, 2010).

## 2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location \\...\cdsesub1evsprod\NDA203188.enx. The information needed for this review was contained in modules 1, 2.7, and 5.3.5.



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# 3 STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

### 3.1.1 Phase 3 Studies: Study 102 and Study 103b

#### *3.1.1.1 Study Design and Endpoints*

Studies 102 and 103b (or Part B) are similar in design. Both are randomized, double blind, placebo-controlled studies to assess the efficacy and safety of 24 weeks of treatment with Ivacaftor 150 mg q12h in subjects age 12 years and older (Study 102) and 6 to 11 years (Study 103b) with cystic fibrosis who have G551D-CFTR mutation in at least 1 allele.

Of note, study 102 was originally planned for a maximum of 24 weeks, but subsequent amendments allowed for a 24 week 'extension' period after the initial 24 week follow-up period in order to investigate the 'durability' of response to treatment. Evaluations were made at baseline, day 15, week 8, week 16, week 24, week 32, week 40, and week 48. In study 103b, the first 24 weeks were the 'treatment' period and the second 24 weeks was the 'extension period' during which the double blind was preserved.

In studies 102 and 103b, subjects were recruited in North America, Europe, and Australia. Inclusion criteria included males and females with 1) a sweat chloride of at least 60 mmol/L or 2-CF-causing mutations and 2) chronic sino-pulmonary disease or GI/nutritional abnormalities. In addition, a predicted normal $FEV_1$ of 40%- 90% and age of at least 12 were required.

**In both Phase 3 studies, the primary efficacy endpoint was the absolute change from baseline in % predicted $FEV_1$ through week 24. The primary method of analysis was Mixed Model Repeated Measures (MMRM) with an 'unstructured' R- matrix and with no imputed data for missing observations**. Covariates were age and baseline % predicted $FEV_1$. The sponsor conducted various sensitivity analyses including using various specified R- matrix structures, ANCOVA and stratified Wilcoxon tests. Other analyses using imputations included last observation carried forward, (LOCF) and worse-case (within subject). The following describes sponsor proposed imputation methods.



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- **LOCF-based analysis:** Missing measurements were imputed as the last non-missing percent predicted $FEV_1$ observation carried forward (LOCF) and analyzed ANCOVA on mean change in percent predicted $FEV_1$ from baseline as the dependent variable, treatment as the main effect, with adjustment for continuous baseline percent predicted $FEV_1$ and continuous baseline age. The mean change in percent predicted $FEV_1$ was the average change from baseline across all post-baseline visits for each subject.
- **Worst-case based analysis:** Missing measurements were imputed as the smallest post-baseline percent predicted $FEV_1$ observation and analyzed using ANCOVA as defined for LOCF-based analysis.
- **Dropout reason-based imputation analysis:** Missing measurements were imputed as the smallest post-baseline percent predicted $FEV_1$ observation for subjects who terminated from treatment prior to the end of the analysis period for any of the following discontinuation reasons: adverse event, noncompliance with study procedures, death, physician decision, and required prohibited medication. Missing values were imputed using LOCF methodology for all other subjects with missing measurements. Results were analyzed using ANCOVA as defined for LOCF-based analysis.
- **Modeling the pattern of missing data:** If the dropout rate was > 10% (either overall or in either treatment group) or if there were inconsistencies between the other sensitivity analyses, Pattern Mixture Model (PMM) [35, 37] was to be used to assess the potential impact of dropout patterns on treatment effect and to assess whether data were missing at random or not. An MMRM model similar to the primary analysis of percent predicted $FEV_1$ included dropout pattern and the interaction between the dropout pattern and treatment and the interaction between dropout pattern and visit as fixed effects. An unstructured covariance matrix was to be assumed. A least-squares estimate for overall treatment effect was to be obtained in each dropout pattern. A pooled estimate of overall treatment effect adjusted for dropout patterns was to be obtained from pattern-specific estimates by a weighted average. Subjects were to be classified based on the last completed visit: Day 15, Week 8, Week 16, and Week 24, etc. Categories were to be collapsed to create meaningful dropout patterns.

Key secondary endpoints were

1. absolute change from baseline in sweat chloride through Week 24
2. absolute change from baseline in CFQ-R (respiratory health domain) through Week 24
3. time to pulmonary exacerbation[1] through Week 48 (study 102 only)
4. change from baseline in weight to Week 48 in study 102 and from baseline to Week 24 in study 103

To control the overall type I error rate, the primary and key secondary endpoints were analyzed in sequence using the following multi-stage gate keeping procedure:

Test 1: The primary efficacy endpoint was tested at significance level $\alpha$=0.05

For Study 102:

[1] Pulmonary exacerbation defined as a change in antibiotic therapy for any 4 or more of the following signs/symptoms: the change in sputum, new or increased hemoptysis, increased cough, increased dyspnea, malaise, fatigue or lethargy, temperature above 38°C, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in lung function by 10%, or radiographic changes indicative of pulmonary infection.



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Test 2: If a statistically significant result was obtained from test 1 then absolute change from baseline in CFQ-R respiratory domain score through Week 24 and change from baseline in sweat chloride through Week 24 was tested using Hochberg's step-up procedure at significance level $\alpha$=0.05

Test 3: If a statistically significant result was obtained from test 2, time to first pulmonary exacerbation through Week 48 and change from baseline in weight through Week 48 was tested using Hochberg's step-up procedure

For Study 103:

Test 2: If a statistically significant result was obtained from test 1 then change from baseline in weight through Week 24 and change from baseline in sweat chloride through Week 24 was tested using Hochberg's step-up procedure at significance level $\alpha$=0.05

Test 3: If a statistically significant result was obtained from test 2, change from baseline in CFQ-R respiratory domain score through Week 24 was tested using Hochberg's step-up procedure

Three different data sets were defined as follows:

**Full Analysis Set (FAS)** was defined as all randomized subjects who received at least 1 dose of study drug (i.e., VX-770 or placebo). The treatment assignment for the FAS was "as randomized," meaning subjects were analyzed according to the treatment groups to which they were randomized, not the study drug actually received. All analyses except for safety used the FAS.

**Per Protocol Set (PPS)** was defined separately for the Week 24 analysis and the Week 48 analysis. The PPS was defined as all FAS subjects without major protocol violations having at least 80% overall study drug compliance as defined in Section 9.7.2.6, and having completed at least 80% of the analysis period. For the Week 24 PPS, subjects having more than 1 missing assessment of $FEV_1$ or who were missing the Week 24 assessment of $FEV_1$ were excluded; for the Week 48 PPS, subjects having more than 1 missing assessment of $FEV_1$ were excluded. Major protocol violations were defined as violations that may have had a substantial impact on efficacy assessments. The criteria used for excluding subjects from the Weeks 24 or 48 PPS were determined and documented before database lock. The PPS analyses were performed for the primary and secondary endpoints to provide supportive evidence for efficacy at Week 24 and Week 48.

**Safety Set** was defined as all subjects who received at least 1 dose of study drug (VX-770 or placebo). The treatment assignment for the Safety Set was "as treated," meaning subjects were analyzed according to the study drug actually received not the study drug to which they were randomized. All analyses of safety were conducted using the Safety Set.



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### *3.1.1.2 Disposition and Baseline Characteristics*

A total of 167 subjects were randomized in Study 102 (84 to ivacaftor and 83 to placebo). Of these, 161 subjects (78 to ivacaftor and 83 to placebo) received at least one dose of the study drug, and are included in the full analysis set. A total of 151 subjects (94%) completed dosing through Week 24 and 148 subjects (90%) completed dosing through Week 48 (Table 1). Given the low dropout rate, handling of missing data should not be an issue.

Table 1: Subject Disposition – Study 102

| Disposition Category | Placebo n (%) | VX-770 n (%) | Overall n (%) |
|---|---|---|---|
| Last Scheduled Visit Completed: | | | |
| Day 1 | 2 (2.6) | 0 | 2 (1.2) |
| Day 15 | 1 (1.3) | 0 | 1 (0.6) |
| Week 8 | 2 (2.6) | 2 (2.4) | 4 (2.5) |
| Week 16 | 2 (2.6) | 1 (1.2) | 3 (1.9) |
| Week 24 | 1 (1.3) | 1 (1.2) | 2 (1.2) |
| Week 32 | 1 (1.3) | 0 | 1 (0.6) |
| Week 40 | 1 (1.3) | 2 (2.4) | 3 (1.9) |
| Week 48 | 68 (87.2) | 77 (92.8) | 145 (90.1) |
| Completed Treatment Period (through Week 24) | 71 (91.0) | 80 (96.4) | 151 (93.8) |
| Failed to Complete Treatment Period | 7 (9.0) | 3 (3.6) | 10 (6.2) |
| Reason for Failing to Complete Treatment Period: | | | |
| Adverse Event | 3 (3.8) | 1 (1.2) | 4 (2.5) |
| Lost to Follow-up | 0 | 0 | 0 |
| Noncompliance with Study Requirements | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Physician Decision | 0 | 0 | 0 |
| Pregnancy | 0 | 1 (1.2) | 1 (0.6) |
| Requires Prohibited Medication | 1 (1.3) | 1 (1.2) | 2 (1.2) |
| Study Termination by Sponsor | 0 | 0 | 0 |
| Withdrawal of Consent | 1 (1.3) | 0 | 1 (0.6) |
| Other [a] | 2 (2.6) | 0 | 2 (1.2) |
| Completed Treatment and Extension Periods (Through Week 48) | 68 (87.2) | 77 (92.8) | 145 (90.1) |
| Failed to Complete Treatment and Extension Periods | 10 (12.8) | 6 (7.2) | 16 (9.9) |
| Reason for Failing to Complete Extension Period: | | | |
| Adverse Event | 4 (5.1) | 1 (1.2) | 5 (3.1) |
| Lost to Follow-up | 0 | 0 | 0 |
| Noncompliance with Study Requirements | 0 | 2 (2.4) | 2 (1.2) |
| Death | 0 | 0 | 0 |
| Physician Decision | 1 (1.3) | 0 | 1 (0.6) |
| Pregnancy | 0 | 1 (1.2) | 1 (0.6) |
| Requires Prohibited Medication | 2 (2.6) | 1 (1.2) | 3 (1.9) |
| Study Termination by Sponsor | 0 | 0 | 0 |
| Withdrawal of Consent | 1 (1.3) | 1 (1.2) | 2 (1.2) |
| Other [a] | 2 (2.6) | 0 | 2 (1.2) |

Source: Study 102 Study Report, page 96



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The table below displays the, treatment group, age and reason for dropout (Table 2).

Table 2: Reason for Discontinuation by treatment group and age– Study 102

| | Group | Time | Age | Reason for leaving study |
|---|---|---|---|---|
| 1 | PLACEBO | DAY 1 | 12 | OTHER: SUBJECT RANDOMIZED BY ERROR |
| 2 | PLACEBO | WEEK 44 | 12 | ADVERSE EVENT: RESPIRATORY FAILURE |
| 3 | PLACEBO | WEEK 32 | 13 | REQUIRES PROHIBITED MEDICATION |
| 4 | PLACEBO | DAY 1 | 18 | OTHER: NEVER DOSED,HE HAD BEEN ILL WITHIN 2WKS |
| 5 | PLACEBO | WEEK 28 | 19 | PHYSICIAN DECISION |
| 6 | PLACEBO | WEEK 12 | 20 | WITHDRAWAL OF CONSENT |
| 7 | PLACEBO | WEEK 20 | 22 | ADVERSE EVENT: INCREASE IN ALT GREATER THAN 5X ULN |
| 8 | PLACEBO | DAY 15 | 23 | ADVERSE EVENT: COMPLETE HEART BLOCK |
| 9 | PLACEBO | DAY 1 | 25 | ADVERSE EVENT: DAILY PANIC ATTACKS SINCE STARTING |
| 10 | PLACEBO | DAY 1 | 27 | OTHER: UPPERRTI D1- INELIGIBLE. NOT DOSED |
| 11 | PLACEBO | DAY 1 | 29 | OTHER: WRONG GENOTYPE PER (b) (4) |
| 12 | PLACEBO | WEEK 16 | 29 | REQUIRES PROHIBITED MEDICATION |
| 13 | PLACEBO | DAY 1 | 29 | OTHER: FEV TOO LOW FOR INCLUSION |
| 14 | PLACEBO | WEEK 12 | 32 | OTHER: INCREASED LAB DRAWS, DIFFICULT LAB STICK |
| 15 | PLACEBO | DAY 1 | 37 | ADVERSE EVENT: PT SICK AT RANDOMIZATION VISIT |
| 16 | VX-770 | WEEK 40 | 12 | NON-COMPLIANCE WITH STUDY REQUIREMENTS |
| 17 | VX-770 | WEEK 8 | 12 | REQUIRES PROHIBITED MEDICATION |
| 18 | VX-770 | WEEK 8 | 16 | ADVERSE EVENT: ELEVATED LIVER ENZYME |
| 19 | VX-770 | WEEK 44 | 16 | NON-COMPLIANCE WITH STUDY REQUIREMENTS |
| 20 | VX-770 | WEEK 28 | 20 | WITHDRAWAL OF CONSENT |
| 21 | VX-770 | DAY -14 | 27 | REQUIRES PROHIBITED MEDICATION |
| 22 | VX-770 | WEEK 20 | 32 | PREGNANCY |



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In Study 103b, a total 52 subjects were randomized and dosed (26 to ivacaftor and 26 to placebo). A total of 49 subjects (94%) completed dosing through Week 24 and 48 subjects (92%) completed dosing through Week 48 (Table 3). Given the low dropout rate, handling of missing data should not be an issue.

Table 3: Subject Disposition – Study 103b

**Table 10-1 Part B: Subject Disposition**

| Status | Placebo n (%) | VX-770 n (%) | Overall n (%) |
|---|---|---|---|
| Randomized Set | 26 | 26 | 52 |
| Safety Set | 26 | 26 | 52 |
| Full Analysis Set (FAS) | 26 | 26 | 52 |
| Week 24 Per Protocol Set (PPS) | 21 | 26 | 47 |
| Week 48 Per Protocol Set (PPS) | 20 | 24 | 44 |
| Last scheduled visit completed: | | | |
| Day 1 | 2 (7.7) | 0 | 2 (3.8) |
| Day 15 | 0 | 0 | 0 |
| Week 8 | 1 (3.8) | 0 | 1 (1.9) |
| Week 16 | 0 | 0 | 0 |
| Week 24 | 0 | 0 | 0 |
| Week 32 | 1 (3.8) | 0 | 1 (1.9) |
| Week 40 | 0 | 0 | 0 |
| Week 48 | 22 (84.6) | 26 (100.0) | 48 (92.3) |
| **Completed Treatment Period (through Week 24)** | 23 (88.5) | 26 (100.0) | 49 (94.2) |
| Failed to complete the Treatment Period | 3 (11.5) | 0 | 3 (5.8) |
| Reason for failing to complete the Treatment Period | | | |
| Adverse event | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Noncompliance with study requirements | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 |
| Pregnancy | 0 | 0 | 0 |
| Required prohibited medication | 1 (3.8) | 0 | 1 (1.9) |
| Study termination by sponsor | 0 | 0 | 0 |
| Withdrawal of consent | 1 (3.8) | 0 | 1 (1.9) |
| Other | 1 (3.8) | 0 | 1 (1.9) |
| **Completed Treatment and Extension Periods (through Week 48)** | 22 (84.6) | 26 (100.0) | 48 (92.3) |
| Failed to complete Treatment Period | 4 (15.4) | 0 | 4 (7.7) |
| Reason for failing to complete Treatment Period | | | |
| Adverse event | 1 (3.8) | 0 | 1 (1.9) |
| Lost to follow-up | 0 | 0 | 0 |
| Noncompliance with study requirements | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 |



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Demographic data and baseline characteristics for the full analysis set are provided in Appendix 2 and Appendix 3. Subject demographic and baseline characteristics were generally similar in the two treatment groups for each study. The majority of subjects were white (98% in Study 102 and 86% in Study 103b). The median age was 24 years in Study 102 and 9 years in Study 103b. Baseline mean percent predicted $FEV_1$ at screening (63.6% in Study 102 and 84.2% in Study 103b), sweat chloride values (100.2 mmol/L in Study 102 and 104.6 mmol/L in Study 103b) and weight (61.5 kg in Study 102 and 30.9 kg in Study 103b) were similar in both treatment groups.

#### *3.1.1.3 Summary of Efficacy Results for Studies 102 and 103b*

A summary of the primary and key secondary efficacy results for Study 102 and Study 103b is provided in Table 4 and Table 5, respectively. In both studies, the results from the analysis of the primary endpoint (absolute change in percent predicted $FEV_1$ through Week 24) showed a statistically significant treatment effect both through Weeks 24 and 48. Analysis of all key secondary endpoints were also statistically significant in favor of ivacaftor in both studies, with the exception of the improvement in CFQ-R respiratory domain score through Week 24 ($p = 0.11$) in Study 103b. Of note, CFQ-R respiratory domain score was the last variable to be tested based on the gatekeeping procedure in Study 103b. Results from the analyses of the primary and key secondary endpoints for each individual study are described in Section 3.1.1.4 and Section 3.1.1.5.

Table 4: Study 102: Results for Primary and Secondary Efficacy Endpoints – Full Analysis Set

| Endpoint | Treatment Difference[a] (95% CI) | *P* value |
|---|---|---|
| **Absolute Change from Baseline in Percent Predicted $FEV_1$ (percentage points)** | | |
| Through Week 24 (Primary Endpoint) | 10.6 (8.6, 12.6) | <0.0001 |
| Through Week 48 | 10.5 (8.5, 12.5) | <0.0001 |
| **Change from Baseline in CFQ-R Respiratory Domain Score (points)[b]** | | |
| Through Week 24 (Key Secondary Endpoint) | 8.1 (4.7, 11.4) | <0.0001 |
| Through Week 48 | 8.6 (5.3, 11.9) | <0.0001 |
| **Change from Baseline in Sweat Chloride (mmol/L)** | | |
| Through Week 24 (Key Secondary Endpoint) | -47.9 (-51.3, -44.5) | <0.0001 |
| Through Week 48 | -48.1 (-51.5, -44.7) | <0.0001 |
| **Time to First Pulmonary Exacerbation** | | |
| Through Week 24 | 0.40 (0.23, 0.71)[c] | 0.0016 |
| Through Week 48 (Key Secondary Endpoint) | 0.46 (0.28, 0.73)[c] | 0.0012 |
| **Change from Baseline in Weight (kg)** | | |
| At Week 24 | 2.8 (1.8, 3.7) | <0.0001 |
| At Week 48 (Key Secondary Endpoint) | 2.7 (1.3, 4.1) | 0.0001 |

Source: Module 2.7.3 Summary of Clinical Efficacy page 25



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Table 5: Study 103b: Results for Primary and Secondary Efficacy Endpoints – Full Analysis Set

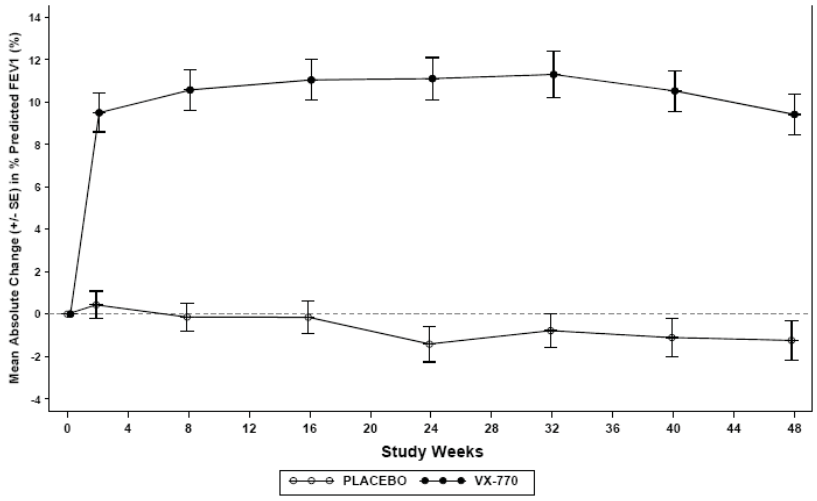
| Endpoint | Treatment Difference[a] (95% CI) | *P* value |
|---|---|---|
| **Absolute Change from Baseline in Percent Predicted $FEV_1$ (percentage points)** | | |
| Through Week 24 (Primary Endpoint) | 12.5 (6.6, 18.3) | <0.0001 |
| Through Week 48 | 10.0 (4.5, 15.5) | 0.0006 |
| **Change from Baseline in CFQ-R (Children Ages 6 to 11) Respiratory Domain Score (points)** | | |
| Through Week 24 (Key Secondary Endpoint) | 6.1 (-1.4, 13.5) | 0.1092 |
| Through Week 48 | 5.1 (-1.6, 11.8) | 0.1354 |
| **Change from Baseline in Sweat Chloride (mmol/L)** | | |
| Through Week 24 (Key Secondary Endpoint) | -54.3 (-61.8, -46.8) | <0.0001 |
| Through Week 48 | -53.5 (-60.9, -46.0) | <0.0001 |
| **Change from Baseline in Weight (kg)** | | |
| At Week 24 (Key Secondary Endpoint) | 1.9 (0.9, 2.9) | 0.0004 |
| At Week 48 | 2.8 (1.3, 4.2) | 0.0002 |

Source: Module 2.7.3 Summary of Clinical Efficacy page 33

### *3.1.1.4 Efficacy Results for Study 102*

In Study 102, treatment with ivacaftor resulted in a significant improvement in percent predicted $FEV_1$ through Week 24 and through Week 48, with treatment difference of 10.6 percentage points and 10.5 percentage points, respectively (Figure 2). The mean absolute change in percent predicted $FEV_1$ from baseline through Week 24 was 10.4 percentage points in the ivacaftor group versus -0.2 percentage points in the placebo group, and through Week 48 was about 10.1 percentage points in the ivacaftor group versus -0.4 percentage points in the placebo group. The results of all sensitivity analyses were consistent with the results of the primary analysis (Table 6).

Figure 2: Mean Absolute Change from Baseline in Percent Predicted $FEV_1$ by Treatment, Full Analysis Set




Source: Figure 14.2.1.1
$FEV_1$: forced expiratory volume in 1 second; SE: standard error
Note: Means were obtained from summary statistics.

Source: Study 102 Study Report page 113



Reference ID: 3071689

Table 6: Study 102: Absolute Change From Baseline in Percent Predicted $FEV_1$, Week 24, Sensitivity Analysis, Full Analysis Set

| | | Overall Absolute Change From Baseline | | Treatment Effect (VX-770 vs Placebo) | |
|---|---|---|---|---|---|
| **Sensitivity Analysis** | **Treatment Group** | **n** | **LS Mean** | **Difference (95% CI)** | ***P*-value** |
| MMRM With Toeplitz Covariance[a] | Placebo | 78 | -0.3971 | | |
| | VX-770 | 83 | 10.6010 | 10.9981 (9.0047, 12.9914) | < 0.0001 |
| MMRM With Compound Symmetry Covariance[a] | Placebo | 78 | -0.4104 | | |
| | VX-770 | 83 | 10.6016 | 11.0120 (9.0179, 13.0060) | < 0.0001 |
| MMRM With First Order Autoregressive Covariance[a] | Placebo | 78 | -0.3777 | | |
| | VX-770 | 83 | 10.6084 | 10.9861 (9.1214, 12.8509) | < 0.0001 |
| ANCOVA[b] | Placebo | 78 | -0.3934 | | |
| | VX-770 | 83 | 10.5875 | 10.9809 (8.9795, 12.9822) | < 0.0001 |
| ANCOVA With LOCF[c] | Placebo | 78 | -0.6482 | | |
| | VX-770 | 83 | 10.5511 | 11.1993 (9.1094, 13.2892) | < 0.0001 |
| ANCOVA With Worst Case Imputation[c] | Placebo | 78 | -0.7317 | | |
| | VX-770 | 83 | 10.4302 | 11.1619 (9.0798, 13.2440) | < 0.0001 |
| ANCOVA With Dropout Reason-based Imputation[c] | Placebo | 78 | -0.6602 | | |
| | VX-770 | 83 | 10.4500 | 11.1102 (9.0274, 13.1930) | < 0.0001 |
| Stratified Wilcoxon[d] | Placebo | 78 | -0.0994 | | |
| | VX-770 | 83 | 9.3603 | | < 0.0001 |

Source: Table 14.2.1.2.3.1

ANCOVA: analysis of covariance; CI: confidence interval; $FEV_1$: forced expiratory volume in 1 second; LOCF: last observation carried forward; LS: least squares; MMRM: Mixed-Effects Model for Repeated Measures.

[a] Estimates were obtained from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit (Day 15, Week 8, Week 16, and Week 24) and treatment group, and adjustment for continuous baseline values of age and percent predicted $FEV_1$, using a Toeplitz, compound symmetric, and AR(1) covariance matrix, as indicated.

[b] ANCOVA on the mean change from baseline through Week 24, with treatment as the main effect, and adjustment for continuous baseline values of age and percent predicted $FEV_1$; missing values were not imputed.

[c] Identical ANCOVA model as (b) with missing values imputed by LOCF method, worst case method, and dropout reason based method, as indicated.

[d] Stratified (by baseline percent predicted $FEV_1$ severity and age group) Wilcoxon rank-sum test of the mean change from baseline. Medians are displayed in the LS Mean column.

Source: Study 102 Study Report page 114



Reference ID: 3071689

The result of the MMRM analyses at 48 weeks is almost identical to that using only the week 48 information in an ANCOVA using the same covariates: age and baseline % predicted $FEV_1$. In particular, the standard error of the treatment difference in both cases is 1.3. The estimated covariance structure of change from baseline over the 7 post- baseline visits is very close to compound symmetry:

| | Mean | Std Dev | (N=148) |
|---|---|---|---|
| DAY 15 | 5.43183 | 8.44866 | |
| WEEK 8 | 5.39353 | 8.81258 | |
| WEEK 16 | 5.68974 | 9.35394 | |
| WEEK 24 | 5.31695 | 10.24894 | |
| WEEK 32 | 5.64864 | 10.25151 | |
| WEEK 40 | 5.16290 | 9.84695 | |
| WEEK 48 | 4.42073 | 9.63591 | |

Correlations

| DAY 15 | WEEK 8 | WEEK 16 | WEEK 24 | WEEK32 | WEEK 40 | WEEK 48 |
|---|---|---|---|---|---|---|
| 1.00000 | 0.75922 | 0.73182 | 0.70116 | 0.71258 | 0.63187 | 0.61599 |
| 0.75922 | 1.00000 | 0.79520 | 0.74085 | 0.71290 | 0.74214 | 0.74502 |
| 0.73182 | 0.79520 | 1.00000 | 0.77779 | 0.68468 | 0.68022 | 0.72210 |
| 0.70116 | 0.74085 | 0.77779 | 1.00000 | 0.76333 | 0.78478 | 0.71696 |
| 0.71258 | 0.71290 | 0.68468 | 0.76333 | 1.00000 | 0.73686 | 0.65577 |
| 0.63187 | 0.74214 | 0.68022 | 0.78478 | 0.73686 | 1.00000 | 0.71995 |
| 0.61599 | 0.74502 | 0.72210 | 0.71696 | 0.65577 | 0.71995 | 1.00000 |

## **'Non-Responders' and 'Responders'**

This reviewer counted 25 ivacaftor subjects who did not achieve a change from baseline of at least 5 percentage points in % predicted $FEV_1$ by week 48. There were 18 from North America, 5 from Europe and 2 from Australia. Examination of baselines and genotype did not reveal any pattern of covariates which may account for 'non-responders'. On the other hand, of those who completed 48 weeks, there were 33 of 78 (43%) ivacaftor subjects who achieved a change of at least 5% at 15 days which persisted through 48 weeks. There was 1 of 69 in the placebo group. The respective numbers for persistence through 24 weeks were 43 (54%) in the ivacaftor group and 2 in the placebo group.

Cumulative percentages of change in % predicted $FEV_1$ at Week 48 is presented in Figure 3. The plot illustrates both the overlap in the group distributions and also the clear separation between them in terms of location.

When baseline % predicted $FEV_1$ is plotted against attained % predicted $FEV_1$, it indicates a very strong correlation (r=0.9) between baseline and attained % predicted $FEV_1$ in each treatment group (Figure 4). Since the standard deviations of baseline and attained are almost identical, the correlation between baseline and change from baseline is very low (r-1 ~ -.1). Figure 5 illustrates the regression lines indicating no treatment by baseline interaction and a treatment difference of approximately 10 percentage points.

Figure 3: Empirical distribution Functions of Change in % Predicted FEV1 (week 48, N=143) – Study 102



Reference ID: 3071689

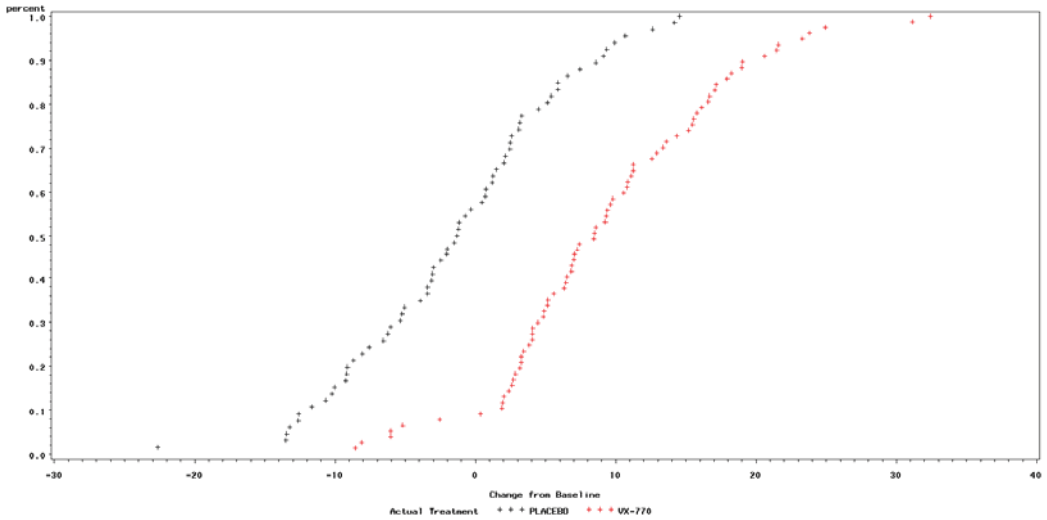



Figure 4: Scatterplot between Attained and Baseline % predicted $FEV_1$ at 48 weeks (completers) – Study 102

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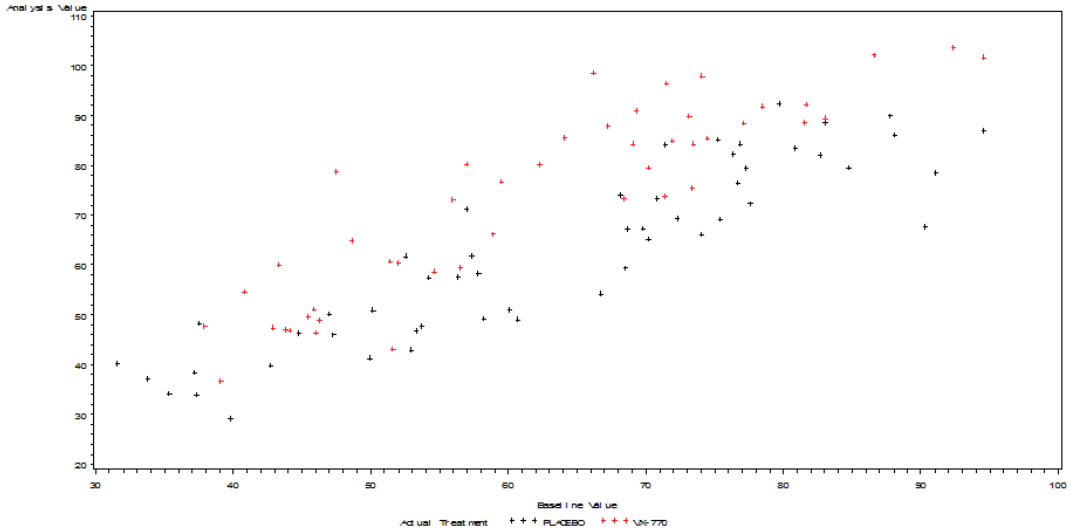


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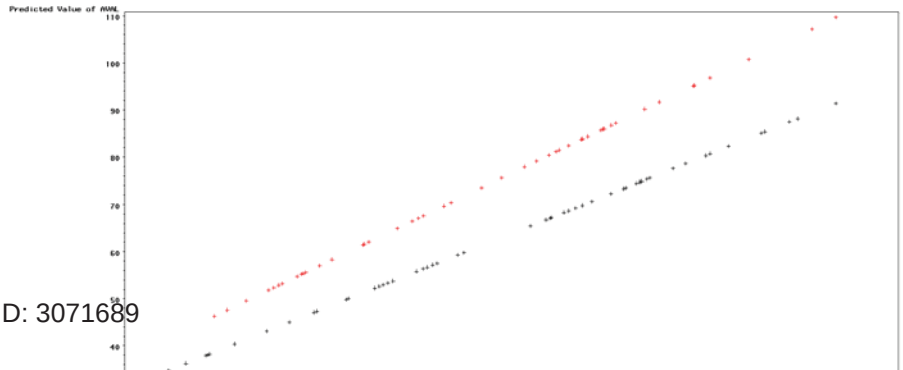
Figure 5: Regression Lines by treatment groups at 48 weeks (completers) – Study 102



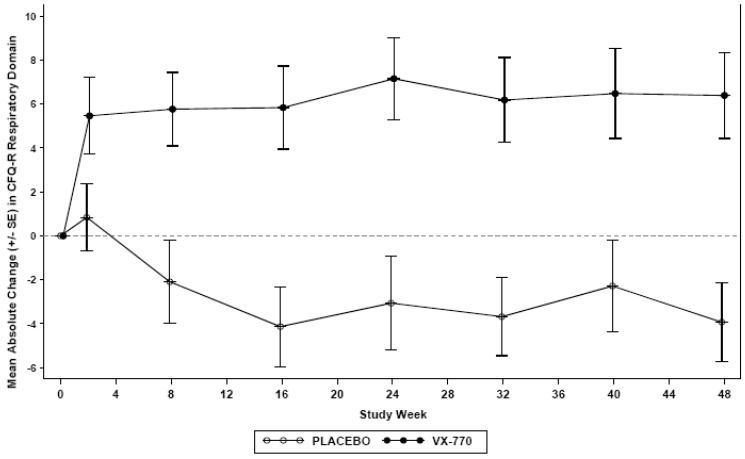



Reference ID: 3071689

**Key Secondary Endpoints:**

The results from the analyses of secondary endpoints are presented in order they were pre-specified. As noted, treatment with ivacaftor resulted in a significant improvement in respiratory domain score of the pooled data from CFQ-R versions for adolescents/adults and for 12 to 13 years of age with a treatment difference of 8.1 points from baseline through Week 24 and 8.6 points from baseline through Week 48 (Figure 6). The mean change in CFQ-R respiratory domain score was 6.0 points in the ivacaftor group versus -2.1 points in the placebo group from baseline through Week 24, and 5.9 points in the ivacaftor group versus -2.7 points in the placebo group from baseline through Week 48. A difference of at least 4 points in the respiratory domain score of the CFQ-R is considered the MCID.

Figure 6: Mean Absolute Change from Baseline in Pooled CFQ-R Respiratory Domain Score by Treatment, Full Analysis Set




Source: Figure 14.2.5.1
CFQ-R: Cystic Fibrosis Questionnaire-Revised; SE: standard error
Note: Means were obtained from summary statistics.

Source: Study 102 Study Report page 118

There is a statistically significant treatment difference in the reduction in sweat chloride concentration (-47.9 mmol/L from baseline through Week 24 and -48.1 mmol/L from baseline through Week 48), Figure 7. The mean change in sweat chloride concentration was -48.7 mmol/L in the ivacaftor group versus -0.8 mmol/L in the placebo group from baseline through Week 24, and -



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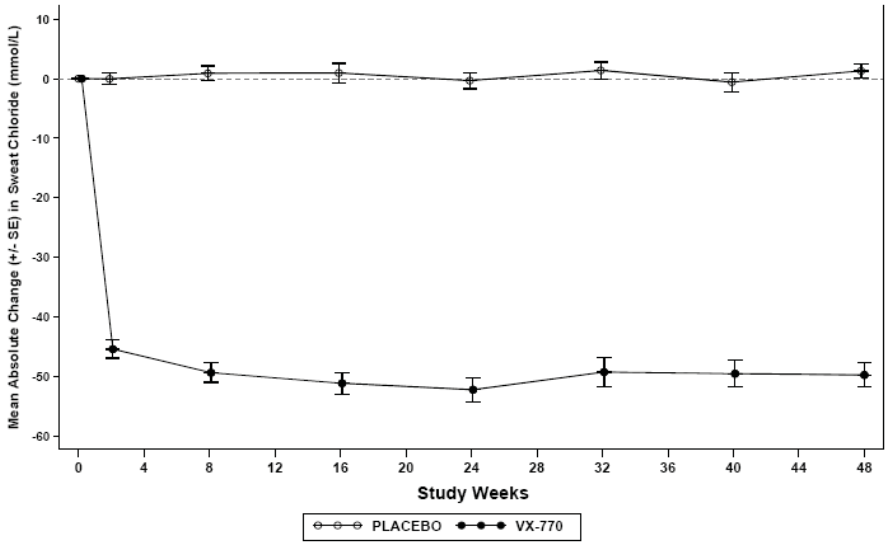
48.7 mmol/L in the ivacaftor group versus -0.6 mmol/L in the placebo group from baseline through Week 48 .

Figure 7: Mean Absolute Change from Baseline in Sweat Chloride by Treatment, Full Analysis Set




Source: Figure 14.2.3.1
SE: standard error
Note: Means were obtained from summary statistics.
Source: Study 102 Study Report page 121

Treatment with ivacaftor resulted in a significant reduction in the risk of pulmonary exacerbation with a 60% reduction in risk of a pulmonary exacerbation from baseline through Week 24 and a 54% reduction in risk of a pulmonary exacerbation from baseline through Week 48 (Figure 8). The pulmonary exacerbation-free rate was 78% in the ivacaftor group versus 51% in the placebo group from baseline through Week 24, and 67% in the ivacaftor group versus 41% in the placebo group from baseline through Week 48.

Figure 8: Time to First Pulmonary Exacerbation by Treatment, Full Analysis Set

Week 24 Week 48



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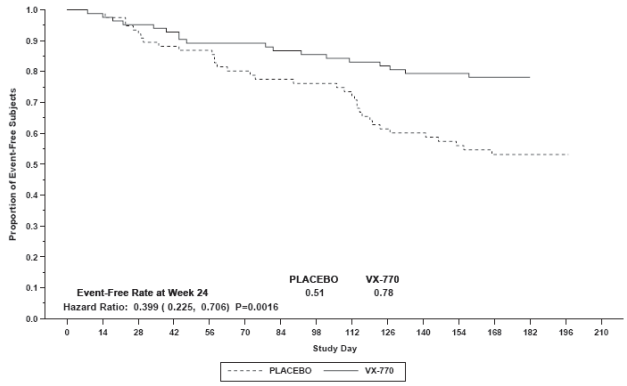
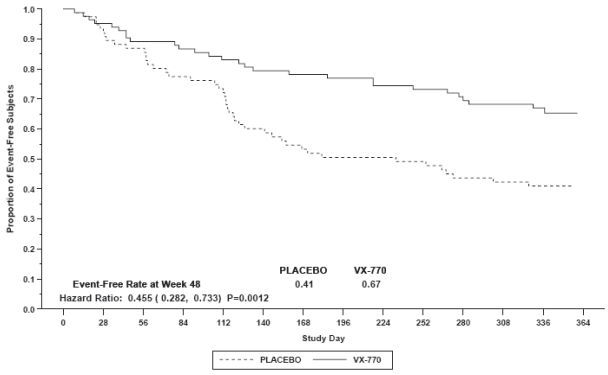
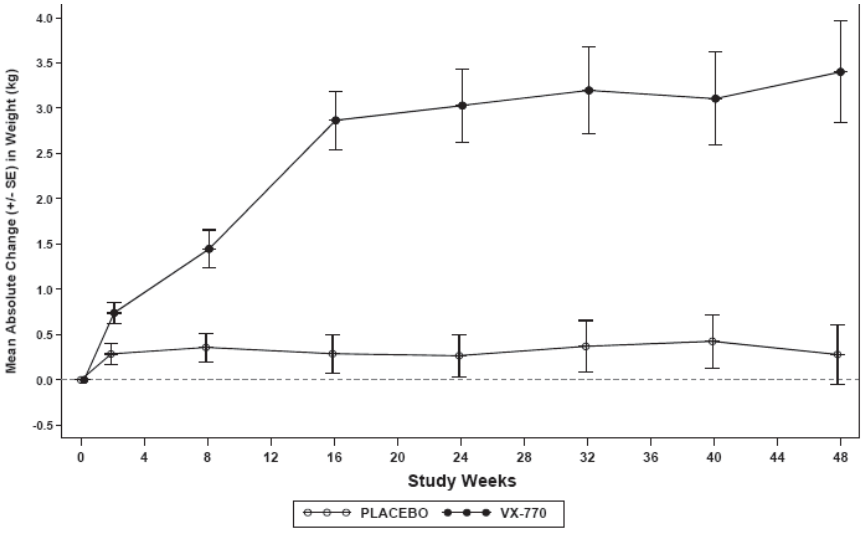



Source: Study 102 Study Report page 123 – 124

Treatment with ivacaftor resulted in a significant increase from baseline in weight, with a treatment difference of 2.8 kg at Week 24 and 2.7 kg at Week 48 (Figure 9). The mean change in weight was 3.0 kg in the ivacaftor group versus 0.2 kg in the placebo group at Week 24, and 3.1 kg in the ivacaftor group versus 0.4 kg in the placebo group at Week 48.

Figure 9: Mean Absolute Change from Baseline in Weight by Treatment, Full Analysis Set




Source: Study 102 Study Report page 125

Cumulative percentages of change in weight at Week 48 is presented in Figure 10. Like the empirical distribution plot for % predicted $FEV_1$, this plot illustrates both the overlap in the group distributions and also the clear separation between them in terms of location.

Figure 10: Empirical Distribution Function for Change in Weight – Study 102

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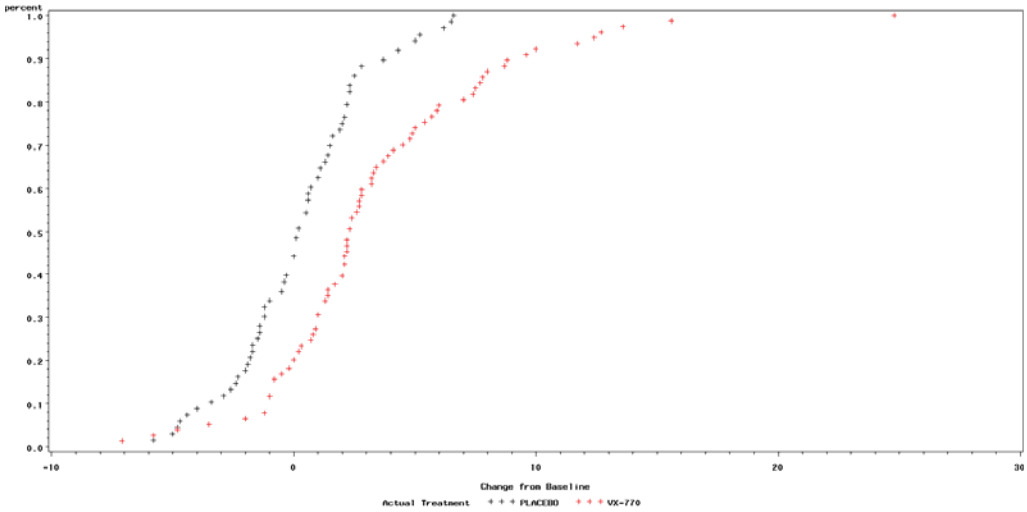
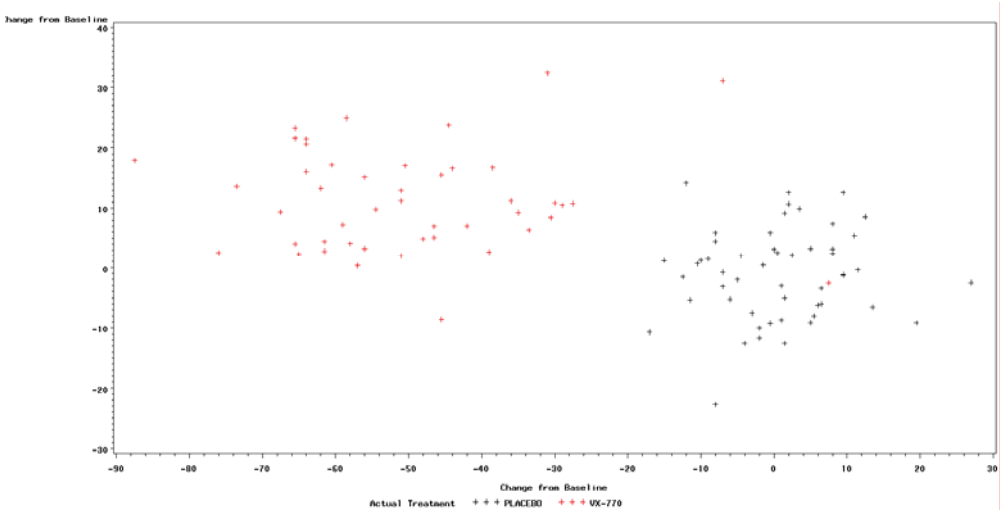



**Additional Analyses:**

There is little if any correlation between change in % predicted $FEV_1$ and change in sweat chloride at 48 weeks in both treatment groups (Figure 11). There is virtually no overlap of the distributions of change in sweat chloride in the two groups. The slight upper-left to lower right trend in the data is due only to the shift in means of the two groups, not the correlation within patients within a group.

Figure 11: Change in % Predicted $FEV_1$ vs Change in Sweat Chloride (48 weeks) – Study 102




There is a convincing average treatment difference of approximately 3 kg in 48 week completers (Table 4 and Figure 9). While change in % predicted $FEV_1$ is correlated with change in weight in each group (r= 0.32, p=0.004), change in % predicted $FEV_1$ is not a good predictor of change in weight (Figure 12).
The poor predictability of weight change given a change in % predicted $FEV_1$ results from the "large" mean squared error (MSE) when weight change is regressed on change in % predicted $FEV_1$.



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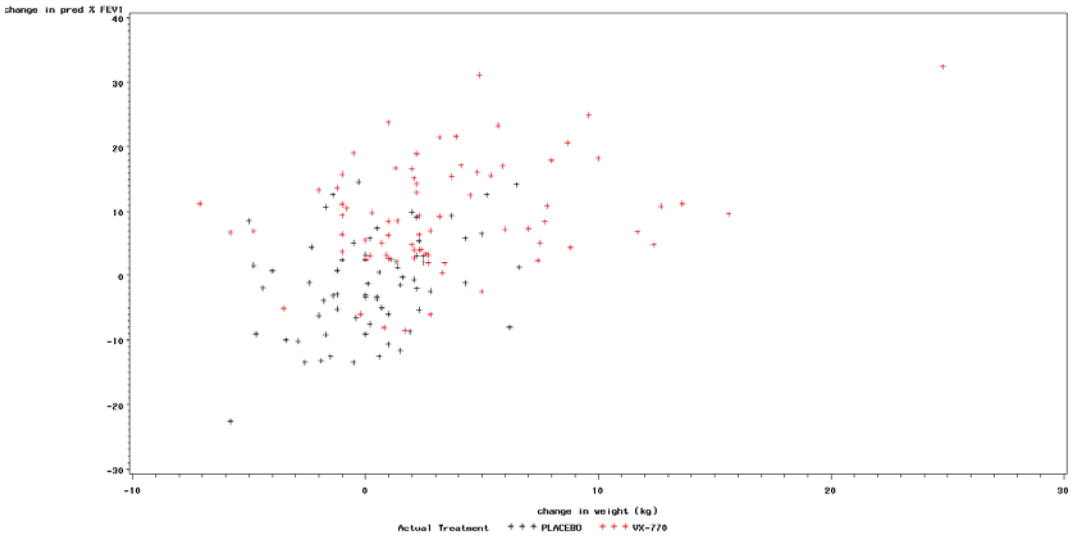
In the ivacaftor group, the root MSE is 4.7, so that a prediction interval for weight change in an independent subject with a mean % predicted $FEV_1$ change of the group average (9.4%) would be 3.4 kg +/- 1.96*4.7 kg= 3.4 kg +/- 9.4 kg, obviously a useless interval given the range in weight change from -8 to +17 when the one outlier of +25 is deleted.

Figure 12: Correlation between change in weight and change in % predicted $FEV_1$ at Week 48

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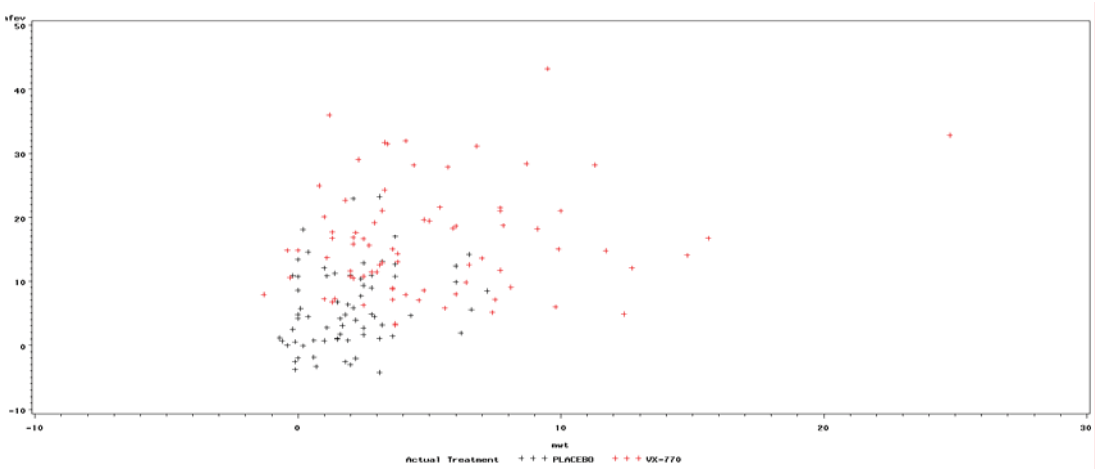
Investigation of any association between the *maximum* change in weight and *maximum* change in % predicted FEV1, demonstrates little or none in the placebo group (Fig 13). In the ivacaftor group, however, there is some evidence, possibly due to its ability to manifest itself through the greater range of values of both changes.

Figure 13: Correlation between MAXIMUM change in weight with MAXIMUM change in % Predicted $FEV_1$



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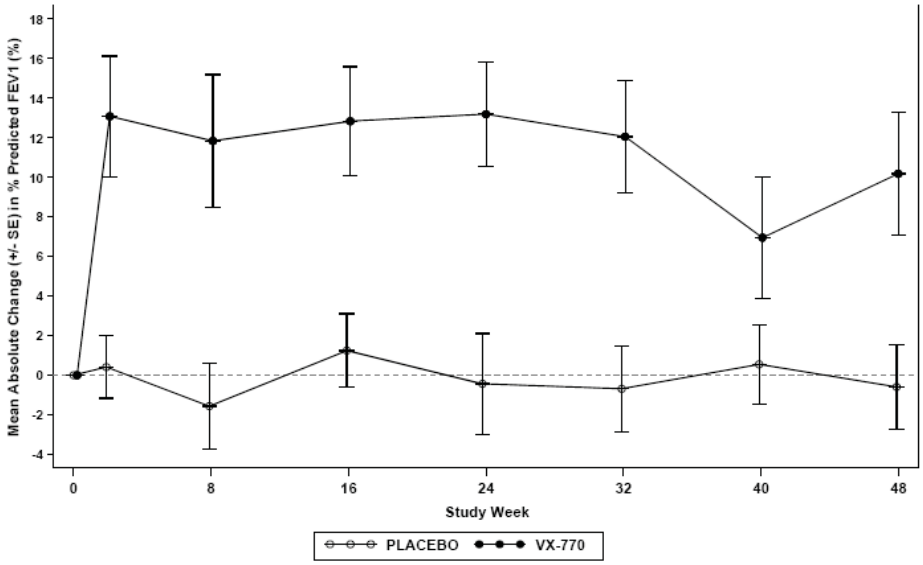
### *3.1.1.5 Efficacy Results for Study 103b*

Like Study 102, treatment with ivacaftor resulted in a significant improvement in percent predicted $FEV_1$ through Week 24 and through Week 48, with treatment difference of 12.5 percentage points and 10.0 percentage points, respectively in Study 103b (Figure 14). The mean absolute change in percent predicted $FEV_1$ from baseline through Week 24 was 12.6 percentage points in the ivacaftor group versus 0.1 percentage point in the placebo group. The results of all sensitivity analyses were consistent with the results of the primary analysis (Table 7).

Figure 14: Mean Absolute Change from Baseline in Percent Predicted $FEV_1$ by Treatment, Full Analysis Set




Source: Figure 14.2.1.1
$FEV_1$: forced expiratory volume in 1 second; SE: standard error
Note: Means were obtained from summary statistics.

Source: Study 103 Clinical Study Report page 134



Reference ID: 3071689

Table 7: Study 103: Absolute Change from Baseline in Percent Predicted $FEV_1$, Week 24, Sensitivity Analysis, Full Analysis Set

| Sensitivity Analysis | Treatment Group | Overall Absolute Change From Baseline | | Treatment Effect (VX-770 vs. Placebo) | |
|---|---|---|---|---|---|
| | | n | LS Mean | Difference (95% CI) | *P* value |
| MMRM with Toeplitz covariance[a] | Placebo | 25 | -0.3127 | -- | -- |
| | VX-770 | 26 | 13.0055 | 13.3183 (7.3138,19.3227) | <0.0001 |
| MMRM with compound symmetry covariance[a] | Placebo | 25 | -0.2707 | -- | -- |
| | VX-770 | 26 | 12.9793 | 13.2500 (7.2258,19.2742) | <0.0001 |
| MMRM with first order autoregressive covariance[a] | Placebo | 25 | -0.3770 | -- | -- |
| | VX-770 | 26 | 13.0442 | 13.4213 (7.7713,19.0712) | <0.0001 |
| ANCOVA[b] | Placebo | 25 | -0.2422 | -- | -- |
| | VX-770 | 26 | 12.9342 | 13.1763 (7.1718,19.1809) | <0.0001 |
| ANCOVA with LOCF[c] | Placebo | 25 | -0.2596 | -- | -- |
| | VX-770 | 26 | 12.9333 | 13.1929 (7.1844,19.2013) | <0.0001 |
| ANCOVA with worst-case imputation[c] | Placebo | 25 | -0.2645 | -- | -- |
| | VX-770 | 26 | 12.9330 | 13.1975 (7.1880,19.2071) | <0.0001 |
| ANCOVA with dropout reason-based imputation[c] | Placebo | 25 | -0.2645 | -- | -- |
| | VX-770 | 26 | 12.9330 | 13.1975 (7.1880,19.2071) | <0.0001 |
| Stratified Wilcoxon[d] | Placebo | 25 | 0.9318 | -- | -- |
| | VX-770 | 26 | 9.4965 | -- | 0.0007 |

Source: Table 14.2.1.2.3.1

ANCOVA: analysis of covariance; CI: confidence interval; $FEV_1$: forced expiratory volume in 1 second; LOCF: last observation carried forward; LS: least squares; MMRM: mixed-effects model for repeated measures

[a] Estimates were obtained from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit (Day 15, Week 8, Week 16, and Week 24) and treatment group, and adjustment for the continuous baseline value of percent predicted $FEV_1$, using a Toeplitz, compound symmetric, and autoregressive of order 1 covariance matrix, as indicated.

[b] ANCOVA on the mean change from baseline through Week 24, with treatment as the main effect, and adjustment for the continuous baseline value of percent predicted $FEV_1$; missing values are not imputed.

[c] Identical ANCOVA model as (b) with LOCF method, worst-case method, and dropout reason-based method, as indicated.

[d] Stratified (by baseline percent predicted $FEV_1$ severity) Wilcoxon rank-sum test of the mean change from baseline. Medians are displayed in the LS Mean column.

Source: Study 103 Clinical Study Report page 135

Change from baseline in % predicted $FEV_1$ are highly correlated across different timepoints (Table 8). The estimated covariance structure of change from baseline over the 7 post- baseline visits is very close to compound symmetry:

Table 8: Correlation structure of Change from Baseline % predicted $FEV_1$

Pearson Correlation Coefficients, N = 47

| | DAY 15 | WK 8 | WK 16 | WK 24 | WK 32 | WK 40 | WK 48 |
|---|---|---|---|---|---|---|---|
| DAY 15 | 1.00000 | 0.80208 | 0.67435 | 0.70173 | 0.71403 | 0.59387 | 0.81083 |
| WK 8 | 0.80208 | 1.00000 | 0.84776 | 0.82141 | 0.77471 | 0.69472 | 0.82150 |
| WK 16 | 0.67435 | 0.84776 | 1.00000 | 0.80654 | 0.67963 | 0.64710 | 0.77283 |
| WK 24 | 0.70173 | 0.82141 | 0.80654 | 1.00000 | 0.81422 | 0.60438 | 0.76511 |
| WK 32 | 0.71403 | 0.77471 | 0.67963 | 0.81422 | 1.00000 | 0.65070 | 0.73625 |
| WK 40 | 0.59387 | 0.69472 | 0.64710 | 0.60438 | 0.65070 | 1.00000 | 0.82252 |
| WK 48 | 0.81083 | 0.82150 | 0.77283 | 0.76511 | 0.73625 | 0.82252 | 1.00000 |

All correlations with p-value < .0001



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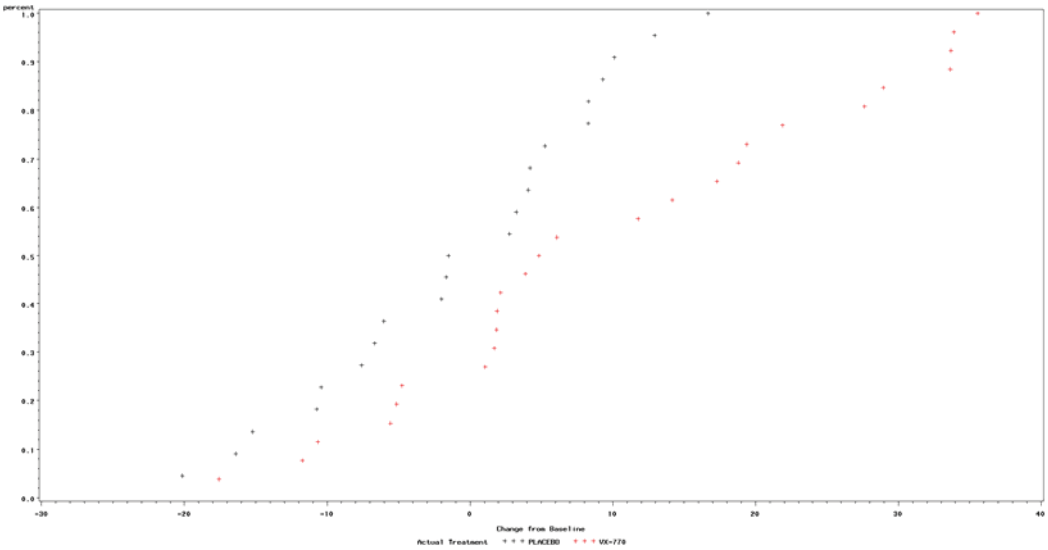
Cumulative percentages of change in % predicted $FEV_1$ at Week 48 is presented in Figure 15. The plot illustrates both the overlap in the group distributions and also the clear separation between them in terms of location.

Figure 15: Empirical distribution Functions of Change in % Predicted FEV1 (week 48) – Study 103

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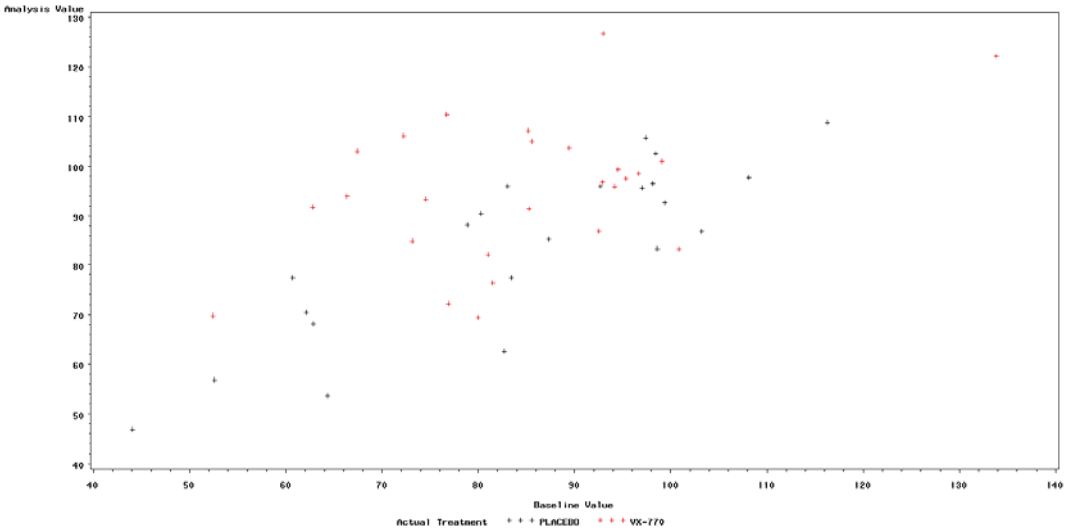
A plot of baseline % predicted $FEV_1$ is plotted against attained % predicted $FEV_1$ indicates a correlation between baseline and attained of r=0.5 in the ivacaftor group and r=0.85 in the placebo group (Figure 16).

Figure 16: Scatterplot between Attained and Baseline % predicted $FEV_1$ at 48 weeks – Study 103b




Note: ANCOVA with baseline and age, p-value=.0023 at Week 48 and p-value =.0003 at 24 weeks.



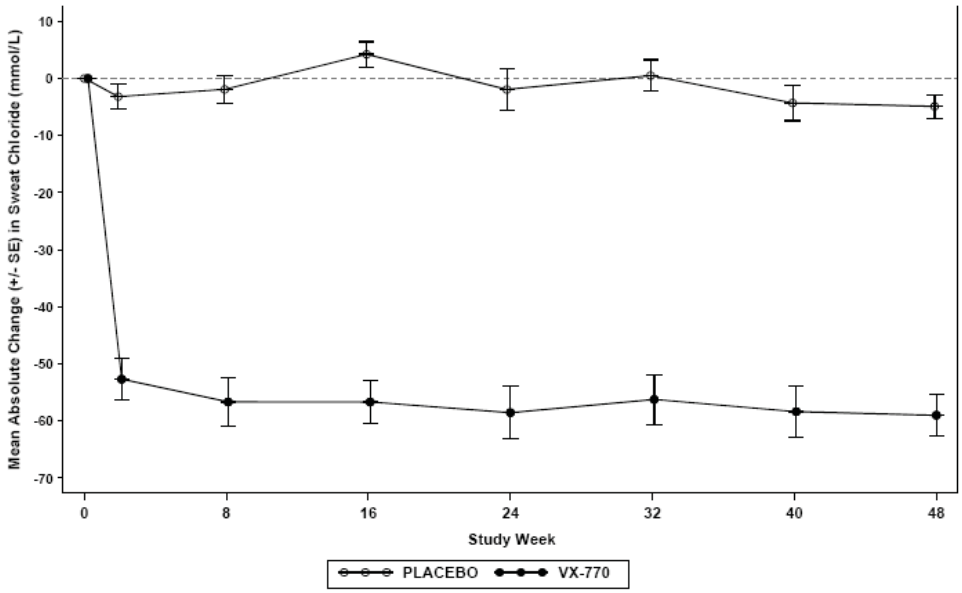
Reference ID: 3071689

**Key Secondary Endpoints:**

The results from the analyses of secondary endpoints are presented in order they were pre-specified.

There is a statistically significant treatment difference in the reduction in sweat chloride concentration (-54.3 mmol/L from baseline through Week 24 and -53.5 mmol/L from baseline through Week 48), Figure 17. The mean change in sweat chloride concentration was -55.5 mmol/L in the ivacaftor group versus -1.2 mmol/L in the placebo group from baseline through Week 24, and -56.0 mmol/L in the ivacaftor group versus -2.6 mmol/L in the placebo group from baseline through Week 48.

Figure 17: Mean Absolute Change from Baseline in Sweat Chloride by Treatment, Full Analysis Set




Source: Figure 14.2.2.1
SE: standard error
Note: Means were obtained from summary statistics.
Source: Study 103 Study Report page 143

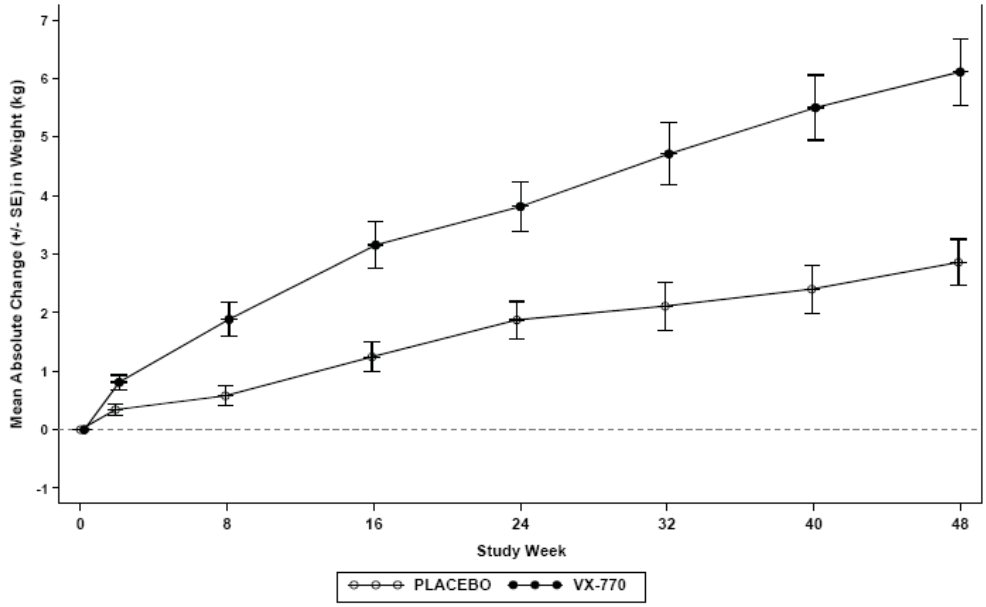
Treatment with ivacaftor resulted in a significant increase from baseline in weight, with a treatment difference of 1.9 kg at Week 24 and 2.8 kg at Week 48 (Figure 18). The mean change in weight was 3.7 kg in the ivacaftor group versus 1.8 kg in the placebo group at Week 24, and 5.9 kg in the ivacaftor group versus 3.1 kg in the placebo group at Week 48.

Cumulative percentages of change in weight at Week 48 is presented in Figure 19. Like the empirical distribution plot for % predicted $FEV_1$, this plot illustrates both the overlap in the group distributions and also the clear separation between them in terms of location.



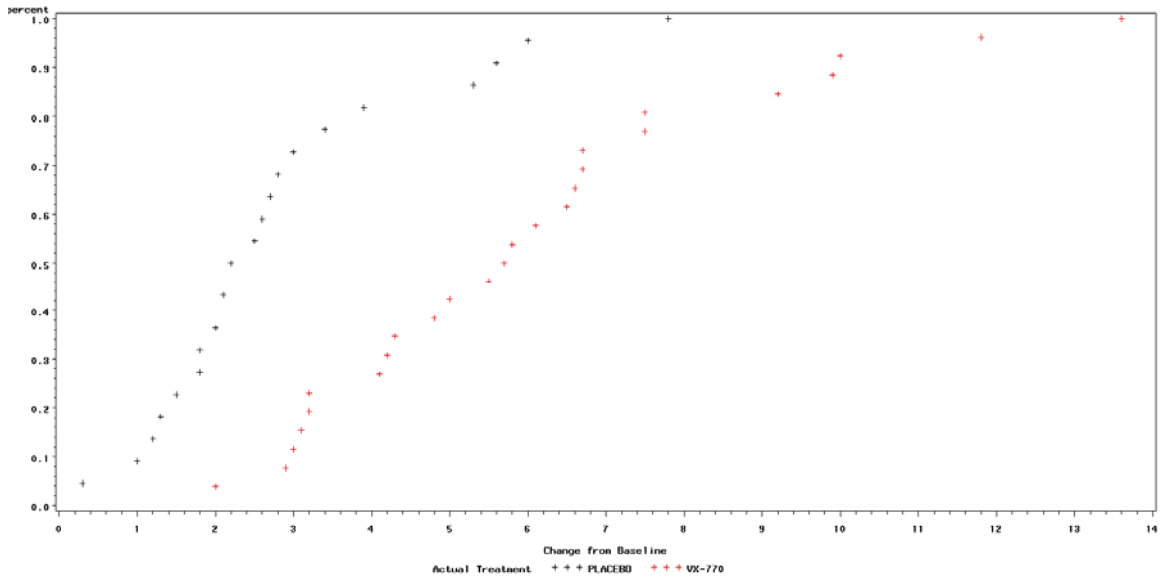
Reference ID: 3071689

Figure 18: Mean Absolute Change from Baseline in Weight by Treatment, Full Analysis Set




Source: Figure 14.2.4.1
SE: standard error
Note: Means were obtained from summary statistics.
Source: Study 103 Study Report page 137

Figure 19: Empirical Distribution Function for Change in Weight – Study 103






Reference ID: 3071689

Two versions of the questionnaire were used: one in which the subject was interviewed (CFQ-R [child], key secondary endpoint) and one in which the subject's parent or caregiver was the respondent (CFQ-R [parent/caregiver]). Although the adjusted mean absolute change from baseline through Week 24 and through Week 48 for the CFQ-R (child) respiratory domain score were numerically greater in the ivafactor group than the placebo group, the estimated treatment differences were not statistically significant (Table 9).

For the CFQ-R (parent/caregiver) respiratory domain score, the adjusted mean absolute change from baseline through Week 24 was statistically significantly greater in the ivafactor group than the placebo group, but the estimated treatment difference through Week 48 also did not reach statistical significance.

Table 9: Mean Absolute Change from Baseline in CFQ-R Respiratory Domain Score by Treatment, Full Analysis Set

| | | Sample Statistics | | Overall Absolute Change From Baseline[a] | | Treatment Effect (VX-770 vs. Placebo) | |
|---|---|---|---|---|---|---|---|
| Visit or Time Period | Treatment Group | n | Mean | n | LS Mean | Difference (95% CI) | *P* value[b] |
| **Children ages 6 to 11 years** | | | | | | | |
| Baseline | Placebo | 26 | 80.13 | -- | -- | -- | -- |
| | VX-770 | 26 | 78.20 | -- | -- | -- | -- |
| Overall postbaseline through Week 24 | Placebo | 23 | 2.17 | 25 | 0.25 | -- | -- |
| | VX-770 | 26 | 4.17 | 26 | 6.31 | 6.06 (-1.41, 13.53) | 0.1092 |
| Overall postbaseline through Week 48 | Placebo | 22 | 0.75 | 25 | 1.00 | -- | -- |
| | VX-770 | 26 | 7.37 | 26 | 6.06 | 5.06 (-1.64, 11.76) | 0.1354 |
| **Parents/Caregivers** | | | | | | | |
| Baseline | Placebo | 26 | 80.77 | -- | -- | -- | -- |
| | VX-770 | 26 | 81.19 | -- | -- | -- | -- |
| Overall postbaseline through Week 24 | Placebo | 23 | -0.72 | 25 | -1.05 | -- | -- |
| | VX-770 | 26 | 6.62 | 26 | 4.88 | 5.93 (0.50, 11.36) | 0.0330 |
| Overall postbaseline through Week 48 | Placebo | 22 | -3.29 | 25 | -1.19 | -- | -- |
| | VX-770 | 26 | 1.66 | 26 | 3.69 | 4.88 (-0.44, 10.20) | 0.0713 |

Source: Table 14.2.3.1.1, Table 14.2.3.2.1.1 and Table 14.2.3.2.1.2
CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; $FEV_1$: forced expiratory volume in 1 second; LS: least squares; MMRM: mixed-effects model for repeated measures

[a] Estimates were obtained from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit through Week 24 (Day 15, Week 8, Week 16, and Week 24) and through Week 48 (Day 15, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48) and treatment group, and adjustment for continuous baseline values of percent predicted $FEV_1$ and domain score, using an unstructured covariance matrix.

[b] *P* value for overall postbaseline is from the main treatment effect.

Source: Study 103b clinical study report, page 135



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### 3.1.2 Phase 2 Study: Study 104

Study 104a (or Part A) is also similar in design to studies 102 and 103b with key differences being the subject population (cystic fibrosis subjects who have the G551D-CFTR mutation in at least 1 allele in studies 102 and 103b; cystic fibrosis subjects who are homozygous for the F508del-CFTR mutation in study 104), the size of the study (at least 167 total randomized subjects in study 102, 52 total randomized subjects in study 103b and 140 total randomized subjects in study 104a), and the study duration (48 weeks in studies 102 and 103b; 16 weeks in study 104a).

This study was a phase 2, double-blind, placebo-controlled study of ivacaftor 150 mg q12h in subjects 12 or older who were homozygous for the F508-CFTR mutation. It was designed with Part A to be 16 weeks with an open label extension (Part B) up to week 112. Part B enrolled only subjects who had 'responded' in Part A as defined by 1) an increase of at least (b) (4) from baseline in % predicted $FEV_1$ and 2) a decrease in sweat chloride concentration of at least (b) (4) at both the Day 15 and Week 8 visits. Only Part A results are given in this document.

Like in Studies 102 and 103b, the primary endpoint was the absolute change from baseline in percent predicted $FEV_1$ through Week 16. The secondary efficacy variables were change from baseline in sweat chloride through Week 16, change from baseline in CFQ-R through Week 16, and rate of change in weight through Week 16. Statistical methods were the same as in Studies 102 and 103. To control the overall type I error rate, the primary and key secondary endpoints were to be analyzed in sequence. First, the primary efficacy endpoint was to be tested at significance level $\alpha = 0.05$. If it was significant, the key secondary endpoints were to be tested using Hochberg's step-up procedure at significance level $\alpha = 0.05$.

A total of 140 subjects were enrolled and randomized at 34 study sites in the US. Of these, 112 subjects were randomized to ivacaftor and 28 subjects to placebo treatment. None of the subjects discontinued the study before receiving their first dose of study drug. Therefore, the FAS included 140 subjects.

A total of 104 (93%) subjects in the ivacaftor group and 26 (93%) subjects in the placebo group completed Part A dosing. The most frequent reason for study drug dosing discontinuation was an adverse event (3%subjects in the ivacaftor group and 7% subjects in the placebo group). Of the 140 subjects, 33 (79%) eligible subjects in ivacaftor group and 5 (83%) eligible subjects in the placebo group rolled over to Part B of the study.

The majority of study subjects in both groups were White (99%). Compared with the placebo group, the ivacaftor group had a higher percentage of females (48% in the ivacaftor group compared with 43% in the placebo group) and a higher mean percent predicted $FEV_1$ at screening (80% in the ivacaftor group compared with 75% in the placebo group). The mean age was slightly lower in the ivacaftor group (22.8 years) than in the placebo group (25.0 years) Mean weight were also lower in the ivacaftor group than in the placebo group. Baseline sweat chloride values were similar between the 2 treatment groups (b) (4) in ivacaftor group compared with (b) (4) L in the placebo group).



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## Efficacy Results

Overall, the trial failed to demonstrate efficacy of ivacaftor in subjects with this genotype (i.e. CF homozygous for the *F508del-CFTR* mutation). There were no significant improvements in adjusted mean absolute change from baseline through Week 16 in percent predicted $FEV_1$ in the ivacaftor group (b) (4)) compared to the placebo group (b) (4) Table 10.

The adjusted mean decrease from baseline through Week 16 in sweat chloride values was numerically greater in the ivacaftor group than in the placebo group. Effect of ivacaftor administration on respiratory symptoms or on weight was not observed in this study.

Table 10: Study 104: Results for Primary and Secondary Efficacy Endpoints – Full Analysis Set

| | Treatment Group | Sample Statistics | | Absolute Change from Baseline | | Treatment Effect (VX-770 versus Placebo | |
|---|---|---|---|---|---|---|---|
| Endpoint | | n | Mean | n | LS Mean | Difference (95% CI) | p-value |
| **Absolute Change from Baseline in Percent Predicted $FEV_1$** | | | | | | | |
| Through 16 weeks | Placebo | (b) (4) | | | | | |
| | VX-770 | | | | | | |
| **Change from Baseline in Sweat Chloride** | | | | | | | |
| Through 16 weeks | Placebo | (b) (4) | | | | | |
| | VX-770 | | | | | | |
| **Change from Baselin** | | | | | | | |
| Through 16 weeks | Placebo | (b) (4) | | | | | |
| | VX-770 | | | | | | |
| **Change from Baseline in Weight (kg)** | | | | | | | |
| Through 16 weeks | Placebo | (b) (4) | | | | | |
| | VX-770 | | | | | | |



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### 3.2 Evaluation of Safety

Dr. Kimberly Witzmann, the Medical Reviewer, conducted the evaluation of the safety data separately. Reader is referred to her review for information regarding the safety profile of the drug.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

A summary of the results from the applicant's subgroup analyses for age, gender, race, and baseline $FEV_1$ are presented in Appendix 4. I conducted additional subgroup analyses in age, genotype and gender for the primary endpoint in Studies 102 and 103 (Table 11). Discrepancies between Table 11 and Apendix 4 are likely due to slight differences in statistical methodology. In general, the treatment comparison between ivacaftor and placebo among the subgroups were similar to the primary efficacy results in the ITT population.

In Study 102, twenty-two percent (22%) of the subjects were under the age of 18 in this study. The test for interaction using the two age categories from ANOVA at **week 24** between treatment and age category yielded a p-value of 0.04. However, an overall test for interaction using the 'continuous' baseline and post-baseline data with ANCOVA yielded a p-value of 0.35. Ultimately, there is no substantial evidence of age by treatment interaction at **week 24**. At Week 48, there is no evidence of interaction. Note that the difference in results between weeks 24 and 48 is primarily due to dropouts in those under 18. The results in those at least 18 are virtually identical at both weeks.

Forty-eight percent (48%) of the subjects were male and 52% female. The tests for interaction from ANOVA at **week 24** between treatment and gender gave a p-value of 0.11 and a p-value of 0.80 at week 48.

There is some interest in whether subjects with the G551D/F508DEL genotype differ from those with the G551D/other genotype. Results for **week 48** are presented in Table 11. The tests for interaction from ANOVA between treatment and genotype gave a p-value of 0.51.

In Study 103b, I did not conduct additional subgroup analyses because an interaction test is not reliable due to small sample size.



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Table 11: Study 102: Subgroup Analysis for the Primary Endpoint – Full Analysis Set

| | Placebo | Ivacaftor | Difference | 95% CI |
|---|---|---|---|---|
| **AGE** | | | | |
| **1° EP through Week 24 (N=157)** | | | | |
| Less than 18 yrs | -1.2 | 15.0 | 17.0 | (11.4, 22.6) |
| At least 18 yrs | -1.5 | 10.1 | 11.6 | (8.6, 14.5) |
| **1° EP through Week 48 (N=146)** | | | | |
| Less than 18 yrs | 1.0 | 12.7 | 11.7 | (6.0, 17.4) |
| At least 18 yrs | -1.9 | 8.6 | 10.5 | (7.6, 13.4) |
| | | | | |
| **GENDER** | | | | |
| **1° EP through Week 24 (N=157)** | | | | |
| Male | -0.4 | 10.6 | 11.0 | (7.2, 14.8) |
| Female | -2.4 | 11.5 | 13.9 | (10.3, 17.5) |
| **1° EP through Week 48 (N=146)** | | | | |
| Male | -1.5 | 9.6 | 11.1 | (7.2, 14.9) |
| Female | -1.0 | 9.3 | 10.3 | (6.7, 14.0) |
| | | | | |
| **GENOTYPE** | | | | |
| **1° EP through Week 48 (N=146)** | | | | |
| G551D/F508DEL | -1.4 | 8.9 | 10.3 | (7.2, 13.3) |
| G551D/other | -0.9 | 11.2 | 12.1 | (6.8, 17.4) |



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# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

During my review of the clinical studies, I found no statistical issues in the applicant's analyses of the data.

In both Phase 3 studies, the results from the analysis of the primary endpoint (absolute change in percent predicted $FEV_1$ through Week 24) showed a statistically significant treatment effect both through Weeks 24 and 48. Analysis of all key secondary endpoints were also statistically significant in favor of ivacaftor in both studies, with the exception of the improvement in CFQ-R respiratory domain score through Week 24 ($p = 0.11$) in Study 103b. Of note, CFQ-R respiratory domain score was the last variable to be tested based on the gatekeeping procedure in Study 103b. Results from the analyses of the primary and key secondary endpoints for each individual study are described in Section 3.1.1.4 and Section 3.1.1.5.

Additional analyses were conducted to explore potential correlation between the primary endpoint and the weight, as well as with sweat chloride. There was a positive correlation between change from baseline % predicted FEV1 and change in weight, but only minimal or none between change from baseline % predicted FEV1 and sweat chloride.

Overall, study 104a failed to demonstrate efficacy of ivacaftor in subjects with CF homozygous for the *F508del-CFTR* mutation.

## 5.2 Conclusions and Recommendations

For the G551D subjects in trials 102 & 103, statistically significant results against placebo were found for the primary endpoint (absolute change in percent predicted $FEV_1$ through week 24) and key secondary endpoints (CFQ-R score through weeks 24 and 48, change in sweat chloride concentration through weeks 24 and 48, time to first pulmonary exacerbation through weeks 24 and 48, and change in weight at weeks 24 and 48). P-values were consistently less than .001. Both trials indicated that the median change from baseline in the primary endpoint was approximately 10% in the Ivacaftor group and zero in the placebo group through 24 and 48 weeks. Trial 104 was unsuccessful in showing efficacy in subjects with the F508del mutation. The average change from baseline in percent predicted $FEV_1$ was only (b) (4) through week 16.



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# 6 APPENDICES

**Appendix 1:**

**The primary analysis was at 24 weeks for the % predicted $FEV_1$. Sample size was determined using the following table by the sponsor:**

**Table 9-3 Power Estimates Under Possible Scenarios of Treatment Effects, Given a Total of 80 Randomized and Evaluable Subjects**

| Absolute Change in Percent Predicted $FEV_1$ | Relative Change in $FEV_1$ From Baseline | Power |
|---|---|---|
| 3.0% | 4.6% | 47% |
| 3.5% | 5.4% | 59% |
| 4.0% | 6.2% | 71% |
| 4.5% | 6.9% | 81% |
| 5.0% | 7.7% | 88% |
| 5.5% | 8.5% | 93% |
| 6.0% | 9.2% | 96% |

Treatment effect = absolute change from baseline in percent predicted $FEV_1$ for VX-770 minus absolute change from baseline in percent predicted $FEV_1$ for placebo. Power estimates were based on 2-sided t-test with $\alpha = 0.05$, assuming a common standard deviation of 7%. Relative treatment effect = 100 × (absolute treatment effect/65), where 65 was the average baseline percent predicted $FEV_1$ observed from Study 101.



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**Appendix 2: Demographic and Baseline Characteristics – Study 102**

**Table 11-1 Demographics and Baseline Characteristics, Full Analysis Set**

| Variable | Placebo N = 78 | VX-770 N = 83 | Overall N = 161 |
|---|---|---|---|
| **Age (years)** | | | |
| n | 78 | 83 | 161 |
| Mean | 24.7 | 26.2 | 25.5 |
| SD | 9.21 | 9.85 | 9.54 |
| Median | 23.0 | 25.0 | 24.0 |
| Minimum | 12 | 12 | 12 |
| Maximum | 53 | 53 | 53 |
| **Age Group (years), n (%)** | | | |
| < 18 | 17 (21.8) | 19 (22.9) | 36 (22.4) |
| ≥ 18 | 61 (78.2) | 64 (77.1) | 125 (77.6) |
| **Geographic Region, n (%)** | | | |
| North America | 50 (64.1) | 50 (60.2) | 100 (62.1) |
| Europe | 19 (24.4) | 23 (27.7) | 42 (26.1) |
| Australia | 9 (11.5) | 10 (12.0) | 19 (11.8) |
| **Percent Predicted $FEV_1$** | | | |
| n | 78 | 83 | 161 |
| Mean | 63.6688 | 63.4622 | 63.5623 |
| SD | 16.83001 | 16.14409 | 16.42858 |
| Median | 67.1890 | 66.1400 | 66.7020 |
| Minimum | 31.570 | 37.289 | 31.570 |
| Maximum | 97.130 | 98.229 | 98.229 |
| **Percent Predicted $FEV_1$, n (%)** | | | |
| < 70% | 45 (57.7) | 49 (59.0) | 94 (58.4) |
| ≥ 70% | 33 (42.3) | 34 (41.0) | 67 (41.6) |
| **Height (cm)** | | | |
| n | 78 | 83 | 161 |
| Mean | 166.47 | 167.68 | 167.09 |
| SD | 10.349 | 10.008 | 10.161 |
| Median | 167.75 | 168.00 | 168.00 |
| Minimum | 142.2 | 142.8 | 142.2 |
| Maximum | 189.8 | 185.0 | 189.8 |
| **Weight (kg)** | | | |
| n | 78 | 83 | 161 |
| Mean | 61.21 | 61.70 | 61.47 |
| SD | 13.926 | 14.257 | 14.056 |
| Median | 58.65 | 58.80 | 58.80 |
| Minimum | 31.9 | 30.2 | 30.2 |
| Maximum | 109.9 | 107.2 | 109.9 |



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| | | | |
|---|---|---|---|
| **Sweat Chloride (mmol/L)** | | | |
| n | 74 | 78 | 152 |
| Mean | 100.13 | 100.35 | 100.24 |
| SD | 10.626 | 9.999 | 10.275 |
| Median | 100.25 | 100.50 | 100.50 |
| Minimum | 58.0 | 74.5 | 58.0 |
| Maximum | 121.5 | 128.0 | 128.0 |
| **Sex, n (%)** | | | |
| Male | 38 (48.7) | 39 (47.0) | 77 (47.8) |
| Female | 40 (51.3) | 44 (53.0) | 84 (52.2) |
| **Race, n (%)** | | | |
| White | 77 (98.7) | 81 (97.6) | 158 (98.1) |
| Black or African American | 0 | 0 | 0 |
| Not Allowed to Ask Per Local Regulations | 1 (1.3) | 2 (2.4) | 3 (1.9) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 77 (98.7) | 81 (97.6) | 158 (98.1) |
| Not Allowed to Ask Per Local Regulations | 1 (1.3) | 2 (2.4) | 3 (1.9) |

Source: Study 102 Study Report, page 100



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**Appendix 3: Demographic and Baseline Characteristics – Study 103b**

**Table 11-2 Part B: Demographics and Baseline Characteristics, Full Analysis Set**

| Variable | Placebo N = 26 | VX-770 N = 26 | Overall N = 52 |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Male | 16 (61.5) | 9 (34.6) | 25 (48.1) |
| Female | 10 (38.5) | 17 (65.4) | 27 (51.9) |
| **Race, n (%)** | | | |
| White | 23 (88.5) | 22 (84.6) | 45 (86.5) |
| Other | 1 (3.8) | 2 (7.7) | 3 (5.8) |
| Not allowed to ask per local regulations | 2 (7.7) | 2 (7.7) | 4 (7.7) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 0 | 1 (3.8) | 1 (1.9) |
| Not Hispanic or Latino | 24 (92.3) | 23 (88.5) | 47 (90.4) |
| Not allowed to ask per local regulations | 2 (7.7) | 2 (7.7) | 4 (7.7) |
| **Age (years)** | | | |
| n | 26 | 26 | 52 |
| Mean (SD) | 8.9 (1.86) | 8.9 (2.00) | 8.9 (1.91) |
| Median | 8.5 | 9.0 | 9.0 |
| Min;max | 6;12 | 6;12 | 6;12 |
| **Age group (years), n (%)** | | | |
| 6 to 8 | 13 (50.0) | 12 (46.2) | 25 (48.1) |
| 9 to 11 | 12 (46.2) | 11 (42.3) | 23 (44.2) |
| >11 | 1 (3.8) | 3 (11.5) | 4 (7.7) |
| **Height (cm)** | | | |
| n | 26 | 26 | 52 |
| Mean (SD) | 132.59 (12.195) | 134.92 (14.378) | 133.75 (13.252) |
| Median | 131.40 | 133.05 | 132.00 |
| Min;max | 110.5;155.8 | 115.0;168.6 | 110.5;168.6 |
| **Weight (kg)** | | | |
| n | 26 | 26 | 52 |
| Mean (SD) | 30.04 (7.159) | 31.81 (9.949) | 30.93 (8.628) |
| Median | 29.70 | 28.15 | 28.60 |
| Min;max | 17.8;46.3 | 18.8;62.6 | 17.8;62.6 |



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| | | | |
|---|---|---|---|
| **Geographic region, n (%)** | | | |
| North America | 15 (57.7) | 12 (46.2) | 27 (51.9) |
| Europe | 5 (19.2) | 6 (23.1) | 11 (21.2) |
| Australia | 6 (23.1) | 8 (30.8) | 14 (26.9) |
| **% predicted $FEV_1$** | | | |
| N | 26 | 26 | 52 |
| Mean (SD) | 83.7407 (20.36540) | 84.7272 (15.82624) | 84.2339 (18.06477) |
| Median | 85.3500 | 85.2140 | 85.2140 |
| Min;max | 44.016;116.272 | 52.404;133.791 | 44.016;133.791 |
| **% predicted $FEV_1$, n (%)** | | | |
| <70% | 8 (30.8) | 4 (15.4) | 12 (23.1) |
| ≥70% to ≤90% | 6 (23.1) | 12 (46.2) | 18 (34.6) |
| >90% | 12 (46.2) | 10 (38.5) | 22 (42.3) |
| **Sweat chloride (mmol/L)** | | | |
| n | 24 | 24 | 48 |
| Mean (SD) | 104.79 (8.872) | 104.31 (14.541) | 104.55 (11.919) |
| Median | 105.00 | 104.75 | 105.00 |
| Min;max | 92.0;121.0 | 54.0;128.0 | 54.0;128.0 |
| **Oxygen saturation (%)** | | | |

Source: Study 103 Study Report, page 100



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## Appendix 4: Subgroup Analyses

**Table 17 Studies 102 and 103: Subgroup Analyses of the Primary and the Key Secondary Endpoints, Full Analysis Set**

| | Treatment Difference Versus Placebo (95% CI) and *P* Value | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Endpoint/ Study** | **<18 years of age** | **≥18 years of age** | **Male** | **Female** | **<70% $FEV_1$** | **Study 102: ≥70% $FEV_1$ Study 103: 70% to 90% $FEV_1$** | **Study 103: >90% $FEV_1$** | **North America** | **Europe** | **Australia** |
| **Number of subjects (ivacaftor/placebo)[a]** | | | | | | | | | | |
| Study 102 | 19/17 | 64/61 | 39/38 | 44/40 | 49/45 | 34/33 | NA | 50/50 | 23/19 | 10/9 |
| Study 103 | NA | NA | 9/15 | 17/10 | 4/8 | 12/6 | 10/11 | 12/14 | 6/5 | 8/6 |
| **Mean absolute change from baseline in percent predicted $FEV_1$ through Week 24** | | | | | | | | | | |
| Study 102 | 11.9289 (5.9474, 17.9104) *P* = 0.0003 | 9.9119 (7.7975, 12.0264) *P*<0.0001 | 10.1832 (6.8488, 13.5176) *P*<0.0001 | 11.8393 (9.4155, 14.2630) *P*<0.0001 | 10.7391 (7.9438, 13.5343) *P*<0.0001 | 10.6033 (7.5299, 13.6768) *P*<0.0001 | NA | 9.0686 (6.4177, 11.7195) *P*<0.0001 | 9.9641 (6.4300, 13.4981) *P*<0.0001 | 17.2920 (7.6256, 26.9584) *P* = 0.0017 |
| Study 103 | NA | NA | 5.1560 (-2.1768, 12.4889) *P* = 0.1585 | 13.8115 (4.2151, 23.4080) *P* = 0.0066 | NC[b] | 9.3260 (-3.1346, 21.7866) *P* = 0.1322 | 6.8926 (-3.7678, 17.5530) *P* = 0.1920 | 5.7689 (-2.5751, 14.1129) *P* = 0.1661 | 24.6497 (6.4433, 42.8562) *P* = 0.0135 | 4.1553 (-3.7099, 12.0204) *P* = 0.2695 |
| **Mean change in sweat chloride from baseline through Week 24 (mmol/L)** | | | | | | | | | | |
| Study 102 | -51.78 (-59.79, -43.78) *P*<0.0001 | -47.06 (-50.98, -43.14) *P*<0.0001 | -40.99 (-45.87, -36.11) *P* < 0.0001 | -54.00 (-58.24, -49.76) *P*<0.0001 | -47.65 (-52.19, -43.11) *P*<0.0001 | -47.62 (-53.04, -42.19) *P*<0.0001 | NA | -48.68 (-52.86, -44.50) *P*<0.0001 | -45.85 (-53.96, -37.74) *P*<0.0001 | -42.92 (-58.19, -27.64) *P*<0.0001 |
| Study 103 | NA | NA | -60.85 (-70.98, -50.72) *P*<0.0001 | -51.35 (-64.31, -38.39) *P*<0.0001 | NC[b] | -50.24 (-66.58, -33.89) *P*<0.0001 | -68.97 (-77.79, -60.15) *P*<0.0001 | -61.96 (-70.47, -53.45) *P*<0.0001 | NC[b] | -54.20 (-75.16, -33.24) *P* = 0.0002 |

| **Endpoint/ Study** | **<18 years of age** | **≥18 years of age** | **Male** | **Female** | **<70% $FEV_1$** | **Study 102: ≥70% $FEV_1$ Study 103: 70% to 90% $FEV_1$** | **Study 103: >90% $FEV_1$** | **North America** | **Europe** | **Australia** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Time to first pulmonary exacerbation through Week 48[c]** | | | | | | | | | | |
| Study 102 | NC[b] | 0.539[d] (0.318, 0.914) *P* = 0.0218 | 0.491[d] (0.229, 1.052) *P* = 0.0673 | 0.431[d] (0.232, 0.801) *P* = 0.0078 | 0.422[d] (0.232, 0.771) *P* = 0.0050 | 0.463[d] (0.204, 1.052) *P* = 0.0659 | NA | 0.487[d] (0.262, 0.905) *P* = 0.0229 | 0.357[d] (0.137, 0.929) *P* = 0.0348 | NC[b] |
| **Mean change from baseline in CFQ-R respiratory domain score through Week 24 (points)[e]** | | | | | | | | | | |
| Study 102 | 9.71 (2.39, 17.03) *P*<0.0110 | 7.11 (3.24, 10.99) *P* = 0.0004 | 6.85 (2.44, 11.26) *P* = 0.0028 | 9.08 (3.76, 14.39) *P* = 0.0011 | 10.64 (5.90, 15.37) *P*<0.0001 | 5.66 (1.36, 9.95) *P* = 0.0107 | NA | 6.58 (2.21, 10.96) *P* = 0.0036 | 9.49 (1.66, 17.31) *P* = 0.0194 | 15.94 (9.16, 22.73) *P* = 0.0002 |
| Study 103 | NA | NA | 6.29 (-6.33, 18.92) *P* = 0.3109 | 5.88 (-6.95, 18.71) *P* = 0.3528 | NC[b] | 9.27 (-4.22, 22.75) *P* = 0.1636 | -1.98 (-10.21, 6.25) *P* = 0.6084 | -0.73 (-13.35, 11.89) *P* = 0.9053 | 15.49 (-9.53, 40.50) *P* = 0.1765 | 7.42 (-13.24, 28.08) *P* = 0.4423 |
| **Mean change from baseline in weight (kg)[f]** | | | | | | | | | | |
| Study 102 | 3.48 (0.18, 6.79) *P* = 0.0391 | 2.55 (1.11, 3.99) *P* = 0.0005 | 2.91 (0.55, 5.27) *P* = 0.0157 | 2.54 (0.97, 4.11) *P* = 0.0016 | 3.40 (1.64, 5.16) *P* = 0.0002 | 1.75 (-0.49, 3.98) *P* = 0.1249 | NA | 3.08 (1.21, 4.95) *P* = 0.0013 | 3.24 (1.07, 5.41) *P* = 0.0036 | -0.23 (-4.21, 3.75) *P* = 0.9093 |
| Study 103 | NA | NA | 2.32 (0.47, 4.17) *P* = 0.0145 | 1.84 (0.60, 3.07) *P* = 0.0041 | NC[b] | 1.29 (-0.22, 2.79) *P* = 0.0920 | 2.59 (0.52, 4.66) *P* = 0.0149 | 2.18 (0.43, 3.92) *P* = 0.0151 | NC[b] | 2.11 (0.60, 3.62) *P* = 0.0072 |

Source: Module 5.3.5.1: VX08-770-102/Table 14.2.1.2.4.1, VX08-770-102/Table 14.2.3.2.3.1, VX08-770-102/Table 14.2.2.2.3.1, VX08-770-102/Table 14.2.6.4.1, VX08-770-102/Table 14.2.6.4.2, VX08-770-102/Table 14.2.6.4.3, VX08-770-102/Table 14.2.6.4.4, VX08-770-102/Table 14.2.4.2.5.2, VX08-770-102/Figure 14.2.7.2.1, VX08-770-102/Figure 14.2.7.2.2, VX08-770-102/Figure 14.2.7.2.3, VX08-770-102/Figure 14.2.7.2.4; VX08-770-103/Table 14.2.1.2.4.1; VX08-770-103/Table 14.2.3.2.2.1; VX08-770-103/14.2.2.2.2.1; VX08-770-103/Table 14.2.4.2.5.1

NA: not applicable; NC: not conducted

[a] Number of subjects in the subgroup analyses of the primary endpoint/number of subjects adjusted for each endpoint analyzed

[b] Not conducted due to small sample size

[c] Key efficacy endpoint in Study 102 only

[d] Hazard ratio

[e] Pooled CFQ-R versions for adolescents/adults and for 12 to 13 years of age in Study 102; child version for subjects 6 to 11 years of age in Study 103

[f] Analysis at Week 48 in Study 102 and at Week 24 in Study 103

Source: Summary of Clinical Efficacy pages 73 - 75



Reference ID: 3071689

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/s/

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DAVID HOBERMAN
01/13/2012

JOAN K BUENCONSEJO
01/13/2012
I concur with Dr. Hoberman's statistical review of NDA 203188 serial number 000 and his conclusions.

THOMAS J PERMUTT
01/13/2012
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CARCINOGENICITY STUDIES

| | |
|---|---|
| **NDA:** | **203188** |
| **Drug Name:** | **Ivacaftor (**hydroxypropyl-methylcellulose acid succinate) |
| **Indication:** | **Treatment of Cystic Fibrosis** |
| **Applicants:** | **Vertex Pharmaceuticals, Inc.** |
| | **Cambridge, Massachusetts** |
| | **CRO:** [redacted] (b) (4) |
| **Date(s):** | **Submitted: 18 October 2011** |
| | **To Reviewer: 25 October 2011** |
| **Review Priority:** | **Accelerated (6 month)** |
| | |
| **Biometrics Division:** | **Division 6** |
| **Statistical Reviewer:** | **Steve Thomson** |
| **Concurring Reviewers:** | **Karl Lin, Ph.D.** |
| | |
| **Medical Division:** | **Pulmonary, Allergy, and Rheumatology Products** |
| **Toxicologist Team:** | **Marci Wood, Ph.D.** |
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**Keywords:** Carcinogenicity, Cox regresson, Kaplan-Meier product limit, Survival analysis, Trend test

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# 1. EXECUTIVE SUMMARY

Reports from two studies, in rats and mice, were provided. Both studies were recently conducted by [redacted] (b) (4) The rat report states that: "This study was designed to assess the carcinogenicity potential of VX-770 [,i.e. Ivacaftor, ] being developed for the treatment of cystic fibrosis, when administered orally to rats for up to 24 months." (page 14 of rat report) The mouse report uses the same expression for mice. (page 15 of mouse report).

## 1.1. Conclusions and Recommendations

The Sponsor describes the drug product as hydroxypropyl-methylcellulose acid succinate [HPMC-AS] suspended in an aqueous solution of 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) and 0.01% w/v simethicone in distilled water) or 0 (HPMC-AS suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS in distilled water), 25, 75 or 200 mg/kg/day VX-770 suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS and 0.01% w/v simethicone in water, at a dose volume of 5 mL/kg/day.

.

Dosing was administered by daily gavage.

**Table 1. Design of Albino Rat Study (dosed at 5 mL/kg/day)**

| Treatment Group[1] | # Animals | Dosage (mg/kg/day) | Concentration (mg/g)[2] |
|---|---|---|---|
| 1. Veh w/ sem. [3] | 75 | 0 | 10 |
| 2. Veh w/o sem. [3] | 75 | 0 | 10 |
| 3. Low | 75 | 5 | 2 |
| 4. Medium | 75 | 15 | 6 |
| 5. High | 75 | 50 | 20 |

[1] Test article (TA) was a 50:49.5:0.5 [redacted] (b) (4) of VX-770 (API) and hydroxypropylmethylcellulose acetate succinate (HPMC-AS) and sodium lauryl sulphate (SLS). The [redacted] (b) (4) was formulated as a suspension in a vehicle consisting of 0.5% w/v methylcellulose. (MC) + 0.5% w/v sodium lauryl sulfate (SLS) + 0.01% w/v simethicone in water. Group 1was the vehicle control consisting of 0.5%methylcellulose and 0.5% sodium lauryl sulphate + 0.01% simethicone; Group 2 was the same vehicle without simethicone.
[2] API (VX-770) concentrations were ½ of the TA concentrations listed here.
[3] Control article (HPMC-AS-HF) added to both vehicles at the highest concentration level used in the TA.

**Table 2. Design of Mouse Study (dosed at 5 mL/kg/day)**

| Treatment Group[1] | # Animals | Dosage (mg/kg/day) | Concentration (mg/g) [2] |
|---|---|---|---|
| 1. Veh w/ sem. [3] | 65 | 0 | 40 |
| 2. Veh w/o sem. [3] | 65 | 0 | 40 |
| 3. Low | 65 | 25 | 10 |
| 4. Medium | 65 | 75 | 30 |
| 5. High | 65 | 200 | 80 |

[1,2] As above
[3] Control article (HPMC-AS-HF) added to both vehicles at the highest concentration level used in the TA. On Days 1-34, HPMC-AS was prepared at 20 mg/g.



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More detailed descriptions of the studies are provided in Section 3.2.1 and 3.2.2 below. In this report the two vehicle groups are sometimes referred to as “control groups” while the other dose groups are referred to as “actual dose groups” or “treated groups.” Simple summary mortality tables are presented in the FDA analysis associated with these sections of the report. The toxicologist recommended that the vehicle group without simethicone be considered the primary reference group for comparisons (please see Section 1.3.1.1 below for a discussion of this issue),

In Appendix 1, Figures A.1.1 and A.1.2 for rats and Figures A.1.3 and A.1.4 for mice, display Kaplan-Meier estimated survival curves for each study group for each species and gender combination. The results of the tests of trend and differences in survival are displayed in Tables 3 and 4 below:

**Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.0077 | 0.0151 | 0.3244 | 0.0994 |
| Homogeneity over Groups 1-4 | 0.1430 | 0.2981 | 0.8583 | 0.7720 |
| No trend over Groups 1, 3-5 | 0.0258 | 0.0228 | 0.0789 | 0.0435 |
| No trend over Groups 2-5 | 0.0379 | 0.0205 | 0.0380 | 0.0095 |
| No Difference Between Groups 1 vs 5 | 0.0234 | 0.0201 | 0.1747 | 0.0756 |
| No Difference Between Groups 2 vs 5 | 0.0179 | 0.0110 | 0.0626 | 0.0075 |
| No Difference Between Groups 1 vs 2 | 0.5192 | 0.9104 | 0.7496 | 0.5242 |

From Figure A.1.1 in Appendix 1, in male rats, there is a clear association of the high dose group with decreasing survival over time relative to the other dose groups. The other dose groups are more closely intertwined. This is consistent with the results of the tests above. For example, in male rats, each of the tests of homogeneity over all five dose groups were statistically significant (logrank p=0.0077, Wilcoxon p= 0.0151), while the test of homogeneity deleting the high dose group was not significant at the usual 0.05 level (logrank p=0.1430, Wilcoxon p= 0.2981). This difference in results seems to be associated with outcome of the tests of trend over groups 3-5 with each vehicle separately treated as the basline zero (logrank p=0.0258, Wilcoxon p= 0.0228 and logrank p=0.0379, Wilcoxon p= 0.0205, respectively). Further, the tests comparing the high dose to each vehicle were all statistically significant (logrank p=0.0234, Wilcoxon p= 0.0201 and logrank p=0.0179, Wilcoxon p= 0.011, respectively), again consistent with the overall lack of homogenenity in survival. Finally there is no evidence of differences in survival between the vehicle groups (logrank p=0.5192, Wilcoxon p= 0.9104).

In female rats results are a bit more complicated. From Figure A.1.2 there still seems to be some association of the high dose group with decreasing survival, but it is not statistically significant at the usual level (logrank p=0.3244, Wilcoxon p= 0.0994). Again, there is no particular evidence of lack of homogeneity in dose groups 1-4 (logrank p=0.8583, Wilcoxon p=



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0.7720). On the other hand, the difference between the high dose group and the remaining dose groups does seem to explain most of the statistically significant or close to significant results in the more powerful tests of dose related trend (Group 1 baseline: logrank p=0.0789, Wilcoxon p= 0.0435, Group 2: logrank p=0.0380, Wilcoxon p= 0.0096). As with male rats, there is no evidence of differences in survival between the vehicle groups (logrank p=0.7496, Wilcoxon p= 0.5242).

**Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.6135 | 0.4767 | 0.6251 | 0.6112 |
| No trend over Groups 1, 3-5 | 0.4572 | 0.5423 | 0.8657 | 0.9095 |
| No trend over Groups 2-5 | 0.2062 | 0.1910 | 0.4682 | 0.4259 |
| No Difference Between Groups 1 vs 5 | 0.4384 | 0.4788 | 0.7891 | 0.8593 |
| No Difference Between Groups 2 vs 5 | 0.1140 | 0.0754 | 0.2057 | 0.2453 |
| No Difference Between Groups 1 vs 2 | 0.4525 | 0.3100 | 0.1309 | 0.2324 |

As with rats, figures A.1.3 and A.1.4, in Appendix 1, provide Kaplan-Meier survival curves for each mouse gender. In both mouse genders the mouse survival curves are generally intertwined. In male mice the vehicle group 2 has the highest survival, generally higher than the high dose group. This seems to explain the close to statistically significant pairwise test between groups 2 and 5 (logrank p=0.1140, Wilcoxon p= 0.0754). No other tests in male mice were close to statistical significance (all $p \geq 0.1940$). In female mice, no tests of homogeneity, trend, or differences were statistically significant (all $p \geq 0.1309$).

Of course in a carcinogenicity study, primary interest is on the occurrence of cancers. The statistical analysis is based on a comparison of tumor incidence over dose groups. Complete tumor incidence tables for each organ are provided in Tables A.2.3 through A.2.6 in Appendix 3 and Tables A.3.2 through A.3.5 in Appendix 3. Table 5, below, displays those organ tumor combinations that had at least one test of trend or pairwise difference from the control group without simethicone (i.e. vehicle group 2) that was statistically significant at the usual 0.05 level. For each species by gender by organ the number of animals analyzed and used in the statistical tests is presented first. The tumor incidence for each organ is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, medium, and low dose groups with control group 2.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman rules discussed in Section 1.3.1.5, below, are often applied. That is, when testing for trend over dose and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors (incidence > 1%) and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. As also discussed in section 1.3.1.4, using these adjustments for other tests, like the trend over the



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vehicle, low, and medium dose groups and the comparison between vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate. The period '.' in these tables denotes the p-values of tests of dose groups with no tumors in any group used in the test. Finally, the following table specifies uses the vehicle without simethecone (i.e. vehicle group 2) as the baseline for tests of trend and pairwise comparisoms, As discussed in Section 1.3.1.1, it would seem that a reasonable case can be made that the baseline should be the vehicle with simethecone (i.e. vehicle group 1). Those tables are included in Appendix 3.

**Table 5. Potentially Statistically Significant Neoplasms in Rats and Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Female Rats | | | | | | | | | | |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| Islet Cell Adenoma/Carcinoma | 2 | 1 | 6 | 1 | 0 | .9580 | 1 | .7305 | .0401 | .8906 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0464 | .1923 | .4839 | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 66 | 69 | | | | | |
| C-CELL ADENOMA | 4 | 1 | 1 | 0 | 4 | .0254 | .1275 | 1 | .7301 | .9752 |
| Male Mice | | | | | | | | | | |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0405 | .2468 | 1 | 1 | .7815 |
| Female Mice | | | | | | | | | | |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| MALIGNANT LYMPHOMA | 14 | 7 | 10 | 17 | 11 | .2266 | .1648 | .0127 | .2514 | .9693 |

First note that no tests in male rats even achieved the usual frequentist 0.05 significance level. In female rats, using the incidence in the vehicle without simethicone group to specify whether a tumor is treated as common or rare (i.e., more or less than 1%), following the Haseman-Lin rules cited above, none of the comparisons above would be described as statistically significant. That is, in islet cell adenoma in the pancreas comparing the low dose to vehicle we fnd $p = 0.0401 > 0.01$. Results for tests of trend are similar. That is, for systemic pooled hemangioma and hemangiosarcoma the $p = 0.0464 > 0.025$, while for c-cell adenoma of the thyroid $p = 0.0254 > 0.005$. Again, after adjusting for multiplicity, no tests were statistically significant.

In mice results are similar. Again, adjusting for multiplicity, the test of trend in benign interstitial cell tumor in male mice was not significant ($p = 0.0405 > 0.005$). In female mice the test comparing the medium dose group to the vehicle without simethicone was also not significant, though close (i.e. $p = 0.0127 > 0.01$). Further, as discussed previously, including such tests will inflates type I error level to some value greater than 10%, possibly considerably above 10%. No other comparisons met the multiplicity/rarity adjusted test significance levels.



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Again, complete incidence tables in both species are provided in tables A.2.3 through A.2.6 in Appendix 2, and tables A.3.2 through A.3.5 in Appendix 3.

## 1.2. Brief Overview of the Studies

This submission had a rat study:

**Study 09-2122 (Sponsor Study VX-770-TX-014): A 24-Month Oral Carcinogenicity Study in Rats,**

and a very similar, mouse study:

**Study 09-2121 (Sponsor Study VX-770-TX-013): A 24-Month Oral Carcinogenicity Study in Mice.**

Both studies were conducted in [redacted] (b) (4)
Somewhat detailed descriptions of these studies are available in Sections 3.2.1 and 3.2.2, below.

## 1.3. Statistical Issues and Findings

### 1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include details on the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

#### 1.3.1.1. Control Groups:

In both studies the Sponsor's studies had two control groups the first with simethicone, the second without. As noted above, dosing was described as follows: vehicle group 1 was "(hydroxypropyl-methylcellulose acid succinate [HPMC-AS] suspended in an aqueous solution of 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) and 0.01% w/v simethicone in distilled water) [while vehicle group 2 was] (HPMC-AS suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS in distilled water)." Actual dose groups were described as "25, 75 or 200 mg/kg/day VX-770 suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS and 0.01% w/v simethicone in water, at a dose volume of 5 mL/kg/day." (page 6 of report)

For determining baseline, untreated tumor rates, clearly the vehicle group 2, without simethicone is closest to no treatment and thus is most appropriate for assessing the baseline, untreated tumor rate, and determining if a tumor can be classified as rare or common. However, apparently the weight adjusted amount of simethicone is relatively constant across vehicle group 1 and the treated groups. If interest is primarily in compound VX-770, it would seem that a reasonable argument could be made vehicle group 1, with simethicone, is the most appropriate



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comparator group for pairwise comparisons and tests of trend. However, after some discussion the toxicologist determined that tests of trend and differences should be based on the vehicle without simethicone, i.e., vehicle group 2 . These results are summarized above, with complete tables in Appendix 2. Results using vehicle group 1 as the comparator group are presented in Appendix 3.

**1.3.1.3. Survival Analysis:**

The survival analyses presented here are based on both the log rank test and the Wilcoxon test comparing survival curves. The log rank tests tend to put higher weight on later events, while the Wilcoxon test tends to weight events more equally, and thus is more sensitive to earlier differences in survival. The logrank test is most powerful when the survival curves track each other, and thus the hazards, i.e., the conditional probability of the event in the next infinitesimal interval, would be roughly proportional. This is the test used by the Sponsor. In the FDA analysis, both tests were used to test both homogeneity of survival among the treatment groups and the effect of dose on trend in survival. Appendix 1 reviews the specific animal survival analyses in more detail. The results of the Sponsor's analysis are summarized in Sections 3.2.1.1 and 3.2.2.1.

**1.3.1.4. Multiplicity of Tests on Survival:**

Using the logrank and Wilcoxon tests, for each gender in rats there are fourteen tests of survival differences. In mice there are twelvet similar tests of survival in each gender. If we were to assume that any set of tests are independent across comparisons, which clearly they are not, and assume that there is absolutely no difference in survival, the probability of at least one statistically significant result in each gender, at the usual 0.05 level, is about 0.51 in rats, and about 0.46 of at least one statistically significant result in each gender in mice. This gives at least some measure of the possible price paid for the multiplicity of hypothesis tests in the frequentist paradigm.

**1.3.1.5. Tests on Neoplasms:**

The Sponsor's analyses use Peto analyses of neoplasms. The analyses in this report are based on poly-k analysis of tumor incidence. The poly-k test is a modification of the original Cochran-Armitage test of trend in response to dose, adjusted for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). Roughly. animals that die early without the tumor under consideration are down-weighted by an amount proportional to the kth power of the ratio of the animal's lifetime to the length of the study. It was noted in the report of the Society of Toxicological Pathology "town hall" meeting in June 2001 that this poly-k modification of the Cochran-Armitage tests of trend has been recommended over the corresponding Peto tests.

**1.3.1.6. Multiplicity of Tests on Neoplasms:**

Frequentist hypothesis testing involves accepting or rejecting hypotheses about the parameters of interest on the basis of the values of some statistic. If one does not provide some sort of multiplicity adjustment to the significance level, the chances of rejecting one or more true null hypothesis increases as the number of such tests increases. To avoid this it is common to



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adjust for multiplicity in hypothesis testing resulting in an adjustment in experiment-wise Type I error (i.e., the probability of rejecting a true null hypothesis). Based on his extensive experience with such carcinogenicity analyses in standard laboratory rodents, for pairwise tests between the high dose group and controls in two species, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Similarly, Lin and Rahman (1998) showed that tests of trend should be tested at a 0.025 level for rare tumors and 0.005 for common tumors. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation).

Significance levels of the pairwise tests between the vehicle groups and the low and medium dose groups are also provided, for both vehicle groups. Including these tests can be expected to increase the overall type I error rate to some level above the rough 10% level. Even if one uses the Haseman-Lin-Rahman rules above, the overall type I error associated with including the tests between the vehicle and the low and medium-low dose groups may be considerably larger than the rough 10% level resulting when these rules are restricted to the test of trend and pairwise differences between the high dose and vehicle.

**1.3.1.7. Validity of the Designs:**

When determining the validity of designs there are two key points:

1) adequate drug exposure,
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that in standard laboratory rodent species, a survival rate of about 25 animals, out of 50 or more animals, between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. Note that as a percentage of animals that survived to week 91, this criterion is not met in the high dose group in either rat gender, but is met in mice. (Please see Tables 14 and 15 on pages 16-17 and Tables 19 and 20 on page 22). Like the other comments in this section this requires the expertise of the toxicologist, but may suggest that the MTD was exceeded in rats.

The mean weight values and derived differences and ratios in the following table were taken directly from the Sponsor's reports ( Rat Table 5, pages 339-352, Mouse Table 5, pages 323-338). The change from baseline in the table below is the simple difference between the means at the specified dates, and thus animals that die are only counted at the study initiation, not at the end of the study.



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**Table 6. Mean Weights and Changes (in g) in Rats**

| Dose Group | Dose mg/kg/ day | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Week | | Change from baseline | % change relative to vehicle 2 | Week | | Change from baseline | % change relative to vehicle 2 |
| | | 1 | 89 | | | 1 | 97 | | |
| 1.Veh w/ sim | 0 | 264.7 | 948.9 | 684.2 | 100.0% | 196.1 | 604.7 | 408.6 | 100.9% |
| 2.Veh w/o sim | 0 | 260.0 | 943.9 | 683.9 | | 194.5 | 599.3 | 404.8 | |
| 3. Low | 5 | 266.9 | 930.3 | 663,4 | 97.0% | 197.7 | 657.2 | 459.5 | 113.5% |
| 4. Medium | 15 | 261.4 | 888.9 | 627.5 | 91.8% | 198.1 | 660.5 | 462.4 | 114.2% |
| 5. High | 50 | 257.3 | 760.7 | 503.4 | 73.6% | 196.9 | 553.7 | 356.8 | 88.1% |

**Table 7. Mean Weights and Changes (in g) in Mice**

| Dose Group | Dose mg/kg/ day | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Week | | Change from baseline | % change relative to vehicle 2 | Week | | Cha nge from baseline | % change relative to vehicle 2 |
| | | 1 | 89 | | | 1 | 97 | | |
| 1.Veh w/ sim | 0 | 57.6 | 744.6 | 687.0 | 100.4% | 26.4 | 443.9 | 417.0 | 102.5% |
| 2.Veh w/o sim | 0 | 57.8 | 741.7 | 683.9 | | 27.0 | 433.9 | 406.9 | |
| 3. Low | 25 | 60.9 | 725.7 | 664.8 | 97.2% | 28.0 | 483.8 | 455.8 | 112.0% |
| 4. Medium | 75 | 58.4 | 687.2 | 628.8 | 92.0% | 28.2 | 490.7 | 462.5 | 113.7% |
| 5. High | 200 | 56.8 | 567.5 | 510.7 | 74.7% | 27.3 | 390.1 | 362.8 | 89.2% |

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag *et al* (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' " From Tables 6 and 7 above, the weight decrement criterion is exceeded in the high dose groups in males of both species. Although this requires the expertise of the toxicologist, this may be evidence that the MTD was exceeded in the high dose group in males of both species.

The Sponsor summarizes food consumption during the rat study as follows: "Food consumption values of VX-770-dosed males and females [in rats] were generally considered comparable to control values. A few sporadic instances of decreased food consumption were noted in females at 50 mg/kg/day versus corresponding control values, but no consistent trends were evident." (page 44 of report) In mice "There were no test article-related effects on food consumption. Statistically significant differences that were observed were attributed to normal biological variability." (page 45 of report)

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. This suggests that a useful way to assess whether or not the MTD was achieved is to measure early mortality not associated with any identified tumor. If this is high in the higher dose groups it suggests that animals tend to die before having time to develop tumors. Tables 8 and 9, below, display the number of animals in



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each dose group that died of a natural death or moribund sacrifice, but did not show any tumors (i.e., the "Event"):

**Table 8. Natural Death with No Identified Tumor in Rats (Male/Female)**

| | 1. Vehicle w/ sim. | 2.Vehicle w/o sim. | 3. Low | 4. Medium | 5. High |
|---|---|---|---|---|---|
| Males Event | 10 | 21 | 12 | 15 | 34 |
| No event | 59 | 48 | 57 | 54 | 35 |
| Females Event | 1 | 2 | 0 | 2 | 22 |
| No event | 68 | 67 | 69 | 67 | 48 |

It appears that in both rat genders the high dose group seems to have more premature deaths without tumor, i.e. evidence the MTD was exceeded. These apparent differences seem to be confirmed by the time adjusted tests ( Both males and females overall: both Logrank and Wilcoxon $p < 0.0001$, Males Vehicle 2 versus High: Logrank $p = 0.0017$, Females Vehicle 2 versus High: both Logrank and Wicoxon $p < 0.0001$).

**Table 9. Natural Death with No Identified Tumor in Mices (Male/Female)**

| | 1. Vehicle w/ sim. | 2.Vehicle w/o sim. | 3. Low | 4.Medium | 5. High |
|---|---|---|---|---|---|
| Males Event | 19 | 15 | 15 | 16 | 14 |
| No event | 46 | 50 | 50 | 49 | 51 |
| Females Event | 10 | 10 | 16 | 10 | 15 |
| No event | 55 | 55 | 49 | 55 | 50 |

In mice there is no particular evidence of an even moderately strong difference of early death without tumors (Males Overall: Logrank $p = 0.9140$, Wilcoxon $p = 0.8642$, Vehicle 2 versus High: Logrank $p = 0.8910$, Wilcoxon $p = 0.7213$, Females Overall: Logrank $p = 0.4329$, Wilcoxon $p = 0.2451$, Vehicle 2 versus High: Logrank $p = 0.2041$, Wilcoxon $p = 0.0892$). Once again, like the other observations above, these require the expertise of the toxicologist, but these tests do not provide evidence that the MTD was exceeded in either mouse gender.

### 1.3.2. Statistical Findings

Please see Section 1.1 above.

## 2. INTRODUCTION

### 2.1. Overview

This submission summarizes the results of two year rat and mouse studies to assess the carcinogenic potential carcinogenic potential of miacalcic following once daily dosing by subcutaneous injection. Both studies were conducted in the early 1990's by (b) (4)



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### 2.2. Data Sources

The Sponsor provided two SAS transport files, both labeled tumor.xpt, containing SAS tumor data sets named tumor.sas7bdat, largely following the standard specifications of the FDA requested format.

## 3. STATISTICAL EVALUATION

### 3.1. Evaluation of Efficacy

NA

### 3.2. Evaluation of Safety

#### 3.2.1. Study Study 09-2122 (Sponsor Study VX-770-TX-014): A 24-Month Oral Carcinogenicity Study in Rats,

STUDY DURATION: 104 Weeks (planned)
EXPERIMENTAL (DOSING) START DATE: 26 March 2009
INTERIM SACRIFICE: Males: 25 March 2010 Females: 26 March 2010
DOSING TERMINATION: Group 5: Males: 5 Dec. 2010 Females; 9 Dec. 2010 Males
Group 3: Males; 29 December 2010
Group 4: Females; 19 January 2011
Group 2: Males; 20 January 2011
Groups 1 to 3: Females; 1, 3, 6 and 9 February 2011
Groups 1 and 4: Males; 1 March 2011
TERMINAL SACRIFICE: Group 5 Males 23 December 2010
Groups 1 to 5: Females 2, 4, 7 and 10 February 2011
Groups 1 to 4: Males 15 to 18, 20, 22 to 26 and 28 Feb. 2011, 1 to 2 March 2011
RAT STRAIN: Sprague Dawley CD® Rats
ROUTE: Daily Subcutaneous Injection
REPORT DATED: 19 August 2011

The basic design of the rat study has three drug dosing groups, a vehicle control with simethicone and a vehicle control dose group without simethicone. As noted above, dosing was terminated early in several dose groups. For analysis these groups were assigned the nominal level despite such early termination. In male rats the high dose group was terminated early (Week 92), as were all female groups (Week 97). Dosing is summarized in Table 10, below, actually a repeat of Table 1:



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**Table 10. Design of Albino Rat Study (dosed at 5 mL/kg)**

| Treatment Group[1] | # Animals | Dosage (mg/kg/day) | Concentration (mg/g)[2] |
|---|---|---|---|
| 1. Veh w/ sem. [3] | 69 | 0 | 10 |
| 2. Veh w/o sem. [3] | 69 | 0 | 10 |
| 3. Low | 69 | 5 | 2 |
| 4. Medium | 69 | 15 | 6 |
| 5. High | 69 | 50 | 20 |

[1] Test article (TA) was a 50:49.5:0.5 [redacted] (b) (4) of VX-770 (API) and hydroxypropylmethylcellulose acetate succinate (HPMC-AS) and sodium lauryl sulphate (SLS). The [redacted] (b) (4) was formulated as a suspension in a vehicle consisting of 0.5% w/v methylcellulose. (MC) + 0.5% w/v sodium lauryl sulfate (SLS) + 0.01% w/v simethicone in water. Group 1was the vehicle control consisting of 0.5%methylcellulose and 0.5% sodium lauryl sulphate + 0.01% simethicone; Group 2 was the same vehicle without simethicone.
[2] API (VX-770) concentrations were ½ of the TA concentrations listed here.
[3] Control article (HPMC-AS-HF) added to both vehicles at the highest concentration level used in the TA.

In addition to the main study animals noted above, in each dose group in each gender there were an additional 9 toxicological study animals, plus 6 animals that were eliminated in a 12 month interim sacrifice. Note that data for neither group of animals were included in the data set provided by the Sponsor, and thus are ignored in the analyses below.

The Sponsor summarized study conduct as follows: "Sprague-Dawley CD® rats (84/sex/group) were gavaged once daily for up to 24 months with 0 (hydroxypropyl-methylcellulose acetate succinate, [HPMC-AS] suspended in an aqueous solution of 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) and 0.01% w/v simethicone in distilled water) or 0, (HPMC-AS suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS in distilled water), 5, 15 or 50 mg/kg/day VX-770 suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS and 0.01% w/v simethicone in water, at a dose volume of 5 mL/kg/day. At the end of the 12-month dosing period up to 6 animals/sex/group were euthanized and necropsied; all surviving animals were euthanized and necropsied near the end of a two year dosing period. Animals designated as Toxicokinetic (TK) animals (9/sex/group) were dosed in the same manner as the main study Toxicity animals and blood samples were collected on Days 1 and at the end of Months 6 and 12 for determination of plasma concentrations of VX-770 and its major metabolites, VRT-837018 (M1, hydroxymethyl-VX-770) and VRT-842917 (M6, VX-770-carboxylate). Parameters evaluated during the study also included: viability, clinical observations, body weights, food consumption, macroscopic observations and microscopic pathology." (page 6 of rat report) The Sponsor notes that dosing was stopped for males dosed at 5 mg/kg/day (i.e. group 3) in Week 93 and in Week 96 for males dosed at 0 mg/kg/day (vehicle group 2, without simethicone) when the total number of males per group reached 20.

Dose levels were justified as follows: "The maximum tolerated dose (MTD) established for chronic oral administration in 13-week (HLS Study No. 06-2929, Vertex Study No. VX-770-TX-001) and 6-month (HLS Study No. 07-2028, Vertex Study No. VX-770-TX-010) rat studies was believed to be <100 mg/kg/day. After 13 weeks of dosing, both 400 and 200 mg/kg/day



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were clearly above MTD due to excessive TA-related mortality and in the 6-month study, both 150 and 100 mg/kg/day were associated with excessive TA-related mortality." (page 24-25 of report)

After a brief initial period animals were housed singly, with food and water available *ad libitum.*

### 3.2.1.1. Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analyses on survivability and tumorigenicity in rats.

**Sponsor's Survival analysis:**

The Sponsor provided the following table showing the percentage of animals surviving at termination is shown in the following table (Sponsor Text Table 10.3-1):

**Table 11. (Text Table 10.3-1): Percentage of Animals Surviving at Terminal Sacrifice[a]**

| **Group** | **1 with simethicone** | **2 without simethicone** | **3 VX-770** | **4 VX-770** | **5 VX-770** |
|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | **0** | **0** | **5** | **15** | **50** |
| **Males** | 30.4 | 20.3 | 21.7 | 39.1 | 21.7[b] |
| **Females** | 27.5 | 27.5 | 36.2 | 24.6 | 24.3 |

[a]Terminal sacrifice commenced in Week 99 for Group 1-4 males, start of week 92 for Group 5 males and Week 97 for females.
[b]Survival was statistically significantly lower than the male control group based on the trend test and the pair-wise comparison.

The Sponsor noted that: "Males dosed at 50 mg/kg/day had statistically significant lower survival in comparison to controls. Dosing for the 50 mg/kg/day males and females was stopped in Week 89 when the number of surviving males and females was reduced to 20. The males in this group remained on study without treatment until Week 91 when the number of surviving males in the group was reduced to 15. [As noted above,] Dosing was stopped for males dosed at 5 mg/kg/day in Week 93 and in Week 96 for males dosed at 0 mg/kg/day (vehicle without simethicone) when the total number of males per group reached 20. The terminal sacrifice for males in both control groups and males dosedwith 5 and 15 mg/kg/day commenced in Week 99 when the number of survivors in the primary vehicle control group (Group 1 with simethicone) reached 20. At termination, survival of males at 5 and 15 mg/kg/day was similar to controls. Dosing was stopped in females dosed at 15 mg/kg/day in Week 95 when the number of survivors reached 20. All females were terminated beginning Week 97 when the number of survivors in the vehicle control group (Group 1) reached 20. There were no statistically significant differences in survival in females dosed at 5, 15 and 50 mg/kg/day in comparison to the control groups.



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"... The primary cause of preterminal death in both males and females was pituitary tumor, mammary tumors in females or was undetermined in both sexes." (page 43-44 of report) Results of the corresponding statistical analysis were summarized as follows:
"Males
The trend test was statistically significant when Groups 1, 3, 4 and 5 were included in the analysis (p=0.025). Upon exclusion of Group 5, the trend test was no longer statistically significant (p=0.901). The pairwise comparison of Group 5 with Group 1 was statistically significant (p=0.031).

"Females
The trend test was not statistically significant when Groups 1, 3, 4 and 5 were included in the analysis (p=0.097). None of the pairwise comparisons were statistically significant." (page 3678 of rat report)

**Sponsor's Tumorigenicity analysis:**

The Sponsor used a standard Peto style analysis of carcinogenicity, with the Haseman-Lin adjustment for multiplicity (please see Section's 1.3.1.5 and 1.3.1.6 ). These results of this analysis were summarized results as follows: "There was no test article related increase in the incidence of tumors in VX-770-dosed Animals.

Neoplasms occurred at similar incidences in control and test article groups or they occurred sporadically with no dose relationship.

The total number of benign and malignant neoplasms and the number of animals with one or more neoplasms were similar or decreased in groups given VX-770 in comparison with groups given control article (Text Table 10.7.2-1)." This table was copied below:

**Table 12. (Text Table: 10.7.2-1) Summary Incidence of Benign and Malignant Neoplasms**

| | **Male** | | | | | **Female** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| VX-770 (mg/kg) | 0 | 0 | 5 | 15 | 50 | 0 | 0 | 5 | 15 | 50 |
| No. animals examined | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 70 |
| **Total Benign Neoplasms** | 63 | 65 | 58 | 57 | 33 | 119 | 115 | 113 | 120 | 64 |
| **Animals with >1 Benign Neoplasms** | 49 | 44 | 45 | 41 | 27 | 63 | 65 | 64 | 65 | 42 |
| **Total Malignant Neoplasms** | 61 | 23 | 42 | 63 | 6 | 64 | 58 | 53 | 31 | 24 |
| **Animals with >1 Malignant Neoplasms** | 21 | 10 | 18 | 18 | 6 | 35 | 27 | 32 | 19 | 17 |

(page 46 of rat report)



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### 3.2.1.2. FDA Reviewer's Results

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

**Survival analysis:**

The following tables (Table 13 for male rats, Table 14 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Animals that died of other causes during the terminal period are included in the preceding, but overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses. Note that in both genders the high dose group was sacrificed early.

**Table 13. Summary of Male Rats Survival (dose at at 2 mg/cm$^2$)**

| Period (Weeks) | Veh w/ Sim. ~ 0 | Veh w/o Sim. ~ 0 | Low 5 mg | Medium 15 mg | High 50 mg |
|---|---|---|---|---|---|
| 1-52 | 5/69[1]<br>92.7%[2] | 7/69<br>89.9% | 8/69<br>88.4% | 6/69<br>91.3% | 15/69<br>78.3% |
| 53-78 | 22/64<br>60.9% | 14/62<br>69.6% | 22/61<br>56.5% | 20/63<br>62,3% | 20/54<br>49.3% |
| 79-92 | 16/44<br>37.7% | 24/48<br>34.8% | 20/39<br>27.5% | 9/43<br>49.3% | 19/34<br>21.7% |
| 93-99 | 5/28<br>30.4% | 10/25<br>20.3% | 4/20<br>21.7% | 7/34<br>39.1% | 0 |
| Terminal [3]<br>99 | 21 | 14 | 15 | 27 | 15 |

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice



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**Table 14. Summary of Female Rat Survival (dose at 2 mg/cm$^2$)**

| Period (Weeks) | Veh w/ Sim. ~ 0 | Veh w/o Sim. ~ 0 | Low 5 mg | Medium 15 mg | High 50 mg |
|---|---|---|---|---|---|
| 1-52 | 5/69[1] 92.7%[2] | 2/69 97.1% | 6/69 91.3% | 1/69 98.5% | 12/69 82.9% |
| 53-78 | 22/64 69.9% | 21/67 66.7% | 25/63 55.1% | 26/68 60.9% | 23/57 50% |
| 79-92 | 14/42 40.6% | 17/46 42.0% | 9/38 42.0% | 19/42 33.3% | 18/34 24.3% |
| 92- 97 | 9/28 27.5% | 10/29 27.5% | 4/29 36.2% | 6/24 24.6% | 0 |
| Terminal [3] 97 | 19 | 19 | 25 | 17 | 17 |

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice

Table 15 below provides the significance levels of the tests of homogeneity and trend over dose groups as proposed in Section 1.3.1.1, above.

**Table 15. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.0077 | 0.0151 | 0.3244 | 0.0994 |
| Homogeneity over Groups 1-4 | 0.1430 | 0.2981 | 0.8583 | 0.7720 |
| No trend over Groups 1, 3-5 | 0.0258 | 0.0228 | 0.0789 | 0.0435 |
| No trend over Groups 2-5 | 0.0379 | 0.0205 | 0.0380 | 0.0095 |
| No Difference Between Groups 1 vs 5 | 0.0234 | 0.0201 | 0.1747 | 0.0756 |
| No Difference Between Groups 2 vs 5 | 0.0179 | 0.0110 | 0.0626 | 0.0075 |
| No Difference Between Groups 1 vs 2 | 0.5192 | 0.9104 | 0.7496 | 0.5242 |

From figure A.1.1 in Appendix 1, in male rats, there is a clear association of the high dose group with decreasing survival over time relative to the other dose groups. The other dose groups are more closely intertwined. This is consistent with the results of the tests above. For example, each of the tests of homogeneity over all five dose groups were statistically significant (logrank p=0.0077, Wilcoxon p= 0.0151), while the test of homogeneity deleting the high dose group was not significant at the usual 0.05 level (logrank p=0.1430, Wilcoxon p= 0.2981). This difference seems too be the primary factor in the tests of trend over groups 3-5 with each vehicle separately treated as the basline zero (logrank p=0.0258, Wilcoxon p= 0.0228 and logrank p=0.0379, Wilcoxon p= 0.0205, respectively). Further, the tests comparing the high dose to each control were all statistically significant (logrank p=0.0234, Wilcoxon p= 0.0201 and logrank p=0.0179, Wilcoxon p= 0.011, respectively), again consistent with the overall lack of homogenenity in survival. Finally, there is no evidence of differences in survival between the vehicle groups (logrank p=0.5192, Wilcoxon p= 0.9104).



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In female rats, results are a bit more complicated. From Figure A.1.2 there still seems to be an association of the high dose group with decreasing survival (logrank p=0.3244, Wilcoxon p=0.0994). Again, there is no particular evidence of lack of homogeneity in dose groups 1-4 (logrank p=0.8583, Wilcoxon p= 0.7720). On the other hand, the difference between the high dose group and the remaining dose groups does seem to explain most of the statistically significant or close to significant results in the more powerful tests of dose related trend (Group 1 baseline: (logrank p=0.0789, Wilcoxon p= 0.0435, Group 2: logrank p=0.0380, Wilcoxon p= 0.0096). . As with male rats, there is no evidence of differences in survival between the vehicle groups (logrank p=0.7496, Wilcoxon p= 0.5242).

**Tumorigenicity analysis:**

As discussed in Section 1.3.1.6, the Haseman-Lin-Rahman rules for adjusting for multiplicity in a two gender, two species for a very rough 0.10 (10%) overall false positive error rate, tests of trend should be tested at a 0.025 (2.5%) level for rare tumors and a 0.005 (0.5%) level for common tumors. Comparisons between the single specified control and the high dose should be tested at a 0.05 (5%) level in rare tumors and at 0.01 (1%) level in common tumors. Those organ-tumor combinations with at least nominally statistically significant result ( $p \leq 0.05$) in mice are summarized below:

**Table 16. Potentially Statistically Significant Neoplasms in Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Female Rats | | | | | | | | | | |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| Islet Cell Adenoma/Carcinoma | 2 | 1 | 6 | 1 | 0 | .9580 | 1 | .7305 | .0401 | .8906 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0464 | .1923 | .4839 | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 66 | 69 | | | | | |
| C-CELL ADENOMA | 4 | 1 | 1 | 0 | 4 | .0254 | .1275 | 1 | .7301 | .9752 |

First note that no tests in male rats even achieved the usual frequentist 0.05 significance level. In female rats, using the incidence in the vehicle without simethicone group to specify whether a tumor is treated as common or rare (i.e., more or less than 1%), following the Haseman-Lin rules cited above, none of the comparisons above would be described as statistically significant. That is, in islet cell adenoma in the pancreas comparing the low dose to vehicle we find $p = 0.0401 > 0.01$. Results for tests of trend are similar. For systemic pooled hemangioma and hemangiosarcoma the $p = 0.0464 > 0.025$, while for c-cell adenoma of the thyroid, $p = 0.0254 > 0.005$.

Complete incidence tables are provided in tables A.2.3 and A.2.4 of Appendix 3 and tables A.3.2 and A.3.3 in Appendix 4.



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### 3.2.2. Study 09-2121 (Sponsor Study VX-770-TX-013): A 24-Month Oral Carcinogenicity Study in Mice

STUDY DURATION: 104 Weeks (planned)
EXPERIMENTAL START DATE (INITIATING DOSING): Males: 16 April 2009
Females: 17 April 2009
DOSING TERMINATION: 19 April 2011
TERMINAL SACRIFICE: 14 - 20 April 2011
MOUSE STRAIN: Albino Mice (Outbred) VAF/Plus Crl:CD-1
ROUTE: Daily Gavage
REPORT DATED: 8 September 2011

Gross aspects of the study designs for the main study animals are summarized below (a repeat of table 2) :

**Table 17. Design of Mouse Study (dosed at 5 mL/kg)**

| Treatment Group[1] | # Animals | Dosage (mg/kg/day) | Concentration (mg/g)[2] |
|---|---|---|---|
| 1. Veh w/ sim.[3] | 65 | 0 | 40 |
| 2. Veh w/o sim.[3] | 65 | 0 | 40 |
| 3. Low | 65 | 25 | 10 |
| 4. Medium | 65 | 75 | 30 |
| 5. High | 65 | 200 | 80 |

[1] Test article (TA) was a 50:49.5:0.5 [redacted] (b) (4) mixture of VX-770 (API) and hydroxypropylmethylcellulose acetate succinate (HPMC-AS) and sodium lauryl sulphate (SLS). The [redacted] (b) (4) was formulated as a suspension in a vehicle consisting of 0.5% w/v methylcellulose. (MC) + 0.5% w/v sodium lauryl sulfate (SLS) + 0.01% w/v simethicone in water. Group 1was the vehicle control consisting of 0.5%methylcellulose and 0.5% sodium lauryl sulphate + 0.01% simethicone; Group 2 was the same vehicle without simethicone.
[2] API (VX-770) concentrations were ½ of the TA concentrations listed here.
[3] Control article (HPMC-AS-HF) added to both vehicles at the highest concentration level used in the TA. On Days 1-34, HPMC-AS was prepared at 20 mg/g.

The Sponsor summarized study conduct as follows: "Albino mice (119/sex/group) were gavaged once daily for up to 24 months with 0 (hydroxypropyl-methylcellulose acid succinate [HPMC-AS] suspended in an aqueous solution of 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) and 0.01% w/v simethicone in distilled water) or 0 (HPMC-AS suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS in distilled water), 25, 75 or 200 mg/kg/day VX-770 suspended in an aqueous solution of 0.5% w/v MC with 0.5% w/v SLS and 0.01% w/v simethicone in water, at a dose volume of 5 mL/kg/day. At the end of the 24-month dosing period all surviving animals were euthanized and necropsied. Satellite animals (54/sex/group) were dosed in the same manner as the main study Toxicity animals and blood samples were collected on Day 1 and at the end of Months 6 and 12 for determination of plasma concentrations of VX-770 and its characterized, major metabolites, VRT-837018 (M1, hydroxymethyl-VX-770) and VRT-842917, (M6,VX-770-carboxylate). Parameters evaluated



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during the study also included: viability, clinical observations, body weights, food consumption, macroscopic observations and microscopic pathology." (page 7 of report)

Dosing was justified as follows: "The maximum tolerated dose (MTD) established for chronic oral administration in mice was believed to be ≤300 mg/kg/day, based on results of a 3-month study (08-2051, VX-770-TX-012). After 3 months of dosing, the 1000 and 600 mg/kg/day dosages were both associated with excessive test article-related mortality." (page 25 of report)

Animals were pair-housed in stainless steel, wire mesh cages during the initial week of stabilization (at least 7 days), but were housed individually in suspended stainless steel wire mesh cages thereafter. Food and water was available *ad libitum*.

### 3.2.1.1. Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigenicity in mice.

**Sponsor's Survival analyisis:**

The Sponsor summarizes results as follows:

**Table 18. (Text Table 10.3-1): Percentage of Animals Surviving at Terminal Sacrifice[a]**

| Group | 1 with simethicone | 2 without simethicone | 3 VX-770 | 4 VX-770 | 5 VX-770 |
|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | **0** | **0** | **25** | **75** | **200** |
| **Males** | 33.8 | 36.9 | 32.3 | 29.2 | 27.7 |
| **Females** | 35.4 | 50.8 | 41.5 | 41.5 | 41.5 |

"Statistical analysis of mortality over the 2 years of the study indicated no differences between the controls and test article groups.

"During Month 3 of the study, 1 vehicle control and 5 males at 25 mg/kg/day were euthanized with clinical signs of moderate to severe abdominal distension and abnormal (labored/gasping) breathing. These findings were attributed to the foamy/soapy nature of the vehicle and aeration of the dose formulations while stirring, causing air to be drawn into the dosing cannula, and inadvertently introduced into the gastrointestinal tract. At macroscopic and microscopic examination, gaseous distension of the gastrointestinal tract was seen in the affected animals and was considered to be the cause of these early euthanasias/deaths. Subsequently, animals were carefully monitored throughout the study for signs of abdominal distension/abnormal breathing and given a dose holiday, if necessary, to prevent excessive mortality during the 2-year study period. Overall, abdominal distension observed during the study occurred throughout all groups including the vehicle control groups, and was unrelated to VX-770 administration." (page 44 of report)



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**Sponsor's Tumorigenicity analysis:**

The Sponsor used a standard Peto style analysis of carcinogenicity, with the Haseman-Lin adjustment for multiplicity (please see Section's 1.3.1.5 and 1.3.1.6 ). These results of this analysis were summarized results as follows: "No test article-related differences between the vehicle control groups and the test article groups were observed. Individual neoplasms occurred with comparable incidences in the control and test article mice or they occurred sporadically. These incidental neoplasms have been seen in control mice of this strain and age used in other studies conducted in this facility.

"Overall, the total number of primary neoplasms and the number of males and females with one or more neoplasms in the vehicle I- control, vehicle II-control, and test article groups were comparable (see Text Table 10.7.3-1)."

The following table was copied from this report:

**Table 19. (Text Table: 10.7.3-1) Summary Incidence of Benign and Malignant Neoplasms**

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | 0* | 0** | 25 | 75 | 200 | 0* | 0** | 25 | 75 | 200 |
| #. animals examined | 69 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 |
| Total Primary Neoplasms | 74 | 81 | 83 | 62 | 78 | 67 | 63 | 58 | 68 | 64 |
| Animals with ≥ 1 Primary Neoplasms | 40 | 43 | 46 | 42 | 48 | 46 | 47 | 44 | 43 | 41 |
| Total Benign Neoplasms | 28 | 30 | 37 | 26 | 32 | 29 | 27 | 35 | 30 | 40 |
| Animals with ≥ 1 Benign Neoplasms | 31 | 22 | 25 | 20 | 22 | 20 | 23 | 29 | 22 | 26 |
| Total Malignant Neoplasms | 113 | 169 | 242 | 161 | 252 | 302 | 151 | 179 | 301 | 169 |
| Animals with >1 Malignant Neoplasms | 30 | 33 | 38 | 31 | 35 | 33 | 29 | 21 | 29 | 22 |

(page 46 of mouse report)

### 3.2.1.2. FDA Reviewer's Results

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

**Survival analysis:**

The following tables (Table 20 for male mice, Table 21 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Animals that died of other causes during the terminal period are included in the preceding, but overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses.



Reference ID: 3063799

**Table 20. Summary of Male Mice Survival (dosed at at 5 mg/kg)**

| (Weeks) | Veh w/ Sim. ~ 0 | Veh w/o Sim. ~ 0 | Low 25 mg | Medium 75 mg | High 200 mg |
|---|---|---|---|---|---|
| 1-52 | 7/65 89.2% | 6/65 90.8% | 10/65 84.6% | 4/65 93.8% | 7/65 89.2% |
| 53-78 | 19/58 60.0% | 12/59 72.3% | 14/55 63.1% | 21/61 61.5% | 19/58 60.0% |
| 79-91 | 8/39 47.7% | 8/47 60.0% | 12/41 44.6% | 12/40 43.1% | 11/39 43.1% |
| 92- 104 | 9/31 33.9% | 15/39 36.9% | 8/29 32.3% | 9/28 29.2% | 10/28 27.7% |
| Terminal[3] 104 | 22 | 24 | 21 | 19 | 18[4] |

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice

**Table 21. Summary of Female Mice Survival (dose at 5 mg/kg)**

| Period (Weeks) | Veh w/ Sim. ~ 0 | Veh w/o Sim. ~ 0 | Low 25 mg | Medium 75 mg | High 200 mg |
|---|---|---|---|---|---|
| 1-52 | 3/65 95.4% | 1/65 98.5% | 7/65 89.2% | 7/65 89.2% | 9/65 86.1% |
| 53-78 | 7/62 84.6% | 9/64 84.6% | 10/58 73.8% | 10/58 73.8% | 7/56 75.4% |
| 79-91 | 15/55 61.5% | 13/55 64.6% | 8/48 64.6% | 13/48 53.8% | 9/49 61.5% |
| 92- 104 | 17/40 35.4% | 9/42 50.8% | 13/42 41.5% | 8/36 41.5% | 13/40 41.5% |
| Terminal[3] 104 | 23 | 33 | 27 | 27 | 27[4] |

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice

The following table, Table 22, summarizes the results from tests comparing survival profiles across study groups in the tumorigenicity data sets:



Reference ID: 3063799

**Table 22. Statistical Significances of Tests of Homogeneity and Trend in Survival**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.6135 | 0.4767 | 0.6251 | 0.6112 |
| No trend over Groups 1, 3-5 | 0.4572 | 0.5423 | 0.8657 | 0.9095 |
| No trend over Groups 2-5 | 0.2062 | 0.1910 | 0.4682 | 0.4259 |
| No Difference Between Groups 1 vs 5 | 0.4384 | 0.4788 | 0.7891 | 0.8593 |
| No Difference Between Groups 2 vs 5 | 0.1140 | 0.0754 | 0.2057 | 0.2453 |
| No Difference Between Groups 1 vs 2 | 0.4525 | 0.3100 | 0.1309 | 0.2324 |

Figures A.1.3 through A.1.4, below, provide survival curves for each mouse gender, where, in both mouse genders the survival curves are generally intertwined. In male mice, the vehicle group 2 has the highest survival, generally higher than the high dose group. This seems to explain the close to statistically significant pairwise test between groups 2 and 5 (logrank p=0.1140, Wilcoxon p= 0.0754). No other tests in male mice were close to statistical significance (all $p \geq 0.1940$). In female mice, no tests of homogeneity, trend, or differences were statistically significant (all $p \geq 0.1309$).

**Tumorigenicity analysis:**

As discussed in Section 1.3.1.4, for common tumors, the Haseman-Lin-Rahman rules for adjusting for multiplicity in a single species study specify that for a very rough 0.10 (10%) overall false positive error rate, tests of trend should be tested at a 0.025 (2.5%) level for rare tumors and a 0.005 (0.5%) level for common tumors. Comparisons between the single specified control and the high dose should be tested at a 0.05 (5%) level in rare tumors and at 0.01 (1%) level in common tumors. Those organ-tumor combinations with at least nominally statistically significant result ( $p \leq 0.05$) in mice are summarized below:

**Table 23. Potentially Statistically Significant Neoplasms in Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Male | | | | | | | | | | |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0405 | .2468 | 1 | 1 | .7815 |
| Female | | | | | | | | | | |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| MALIGNANT LYMPHOMA | 14 | 7 | 10 | 17 | 11 | .2266 | .1648 | .0127 | .2514 | .9693 |

Again, adjusting for multiplicity, the test of trend in benign interstitial cell tumor in male mice was not significant ($p = 0.0405 > 0.005$). In female mice the test comparing the medium dose group to the vehicle without simethicone was also not significant, though close (i.e. $p = 0.0127 > 0.01$). Further, as discussed previously, including such tests will inflates type I error level to some value greater than 10%, possibly considerably above 10%. No other comparisons met the multiplicity/rarity adjusted test significance levels.



Reference ID: 3063799

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

**NA**

# 5. SUMMARY AND CONCLUSIONS

## 5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

## 5.2. Conclusions and Recommendations

Please see Section 1.1 above.



Reference ID: 3063799

# APPENDICES

## Appendix 1. FDA Survival Analysis

Simple summary life tables in mortality are presented in the report (Tables 13, 14, 20, and 21, above). Kaplan-Meier estimated survival curves across study groups for each gender are displayed below in Figures A.1.1 and A.1.2 for rats and Figures A.1.3 and A.1.4 for mice. These plots include 95% confidence intervals around each survival curve (colored area around each curve). These plots are also supported by tests of homogeneity in survival over the different treatment groups, tests of trend in survival over increasing dose over the groups with the each vehicle group as the baseline (dropping the other vehicle group), and the results of pairwise comparisons between the high dose group and each vehicle and a comparison between vehicles. The statistical significance levels (i.e., p-values) are provided in Tables A.1.1. and A.1.2., below. One might note that the log rank tests places greater weight on later events, while the Wilcoxon test tends to weight them more equally, and thus places more weight on earlier events than does the log rank test.

**Table A.1.1. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.0077 | 0.0151 | 0.3244 | 0.0994 |
| Homogeneity over Groups 1-4 | 0.1430 | 0.2981 | 0.8583 | 0.7720 |
| No trend over Groups 1, 3-5 | 0.0258 | 0.0228 | 0.0789 | 0.0435 |
| No trend over Groups 2-5 | 0.0379 | 0.0205 | 0.0380 | 0.0095 |
| No Difference Between Groups 1 vs 5 | 0.0234 | 0.0201 | 0.1747 | 0.0756 |
| No Difference Between Groups 2 vs 5 | 0.0179 | 0.0110 | 0.0626 | 0.0075 |
| No Difference Between Groups 1 vs 2 | 0.5192 | 0.9104 | 0.7496 | 0.5242 |

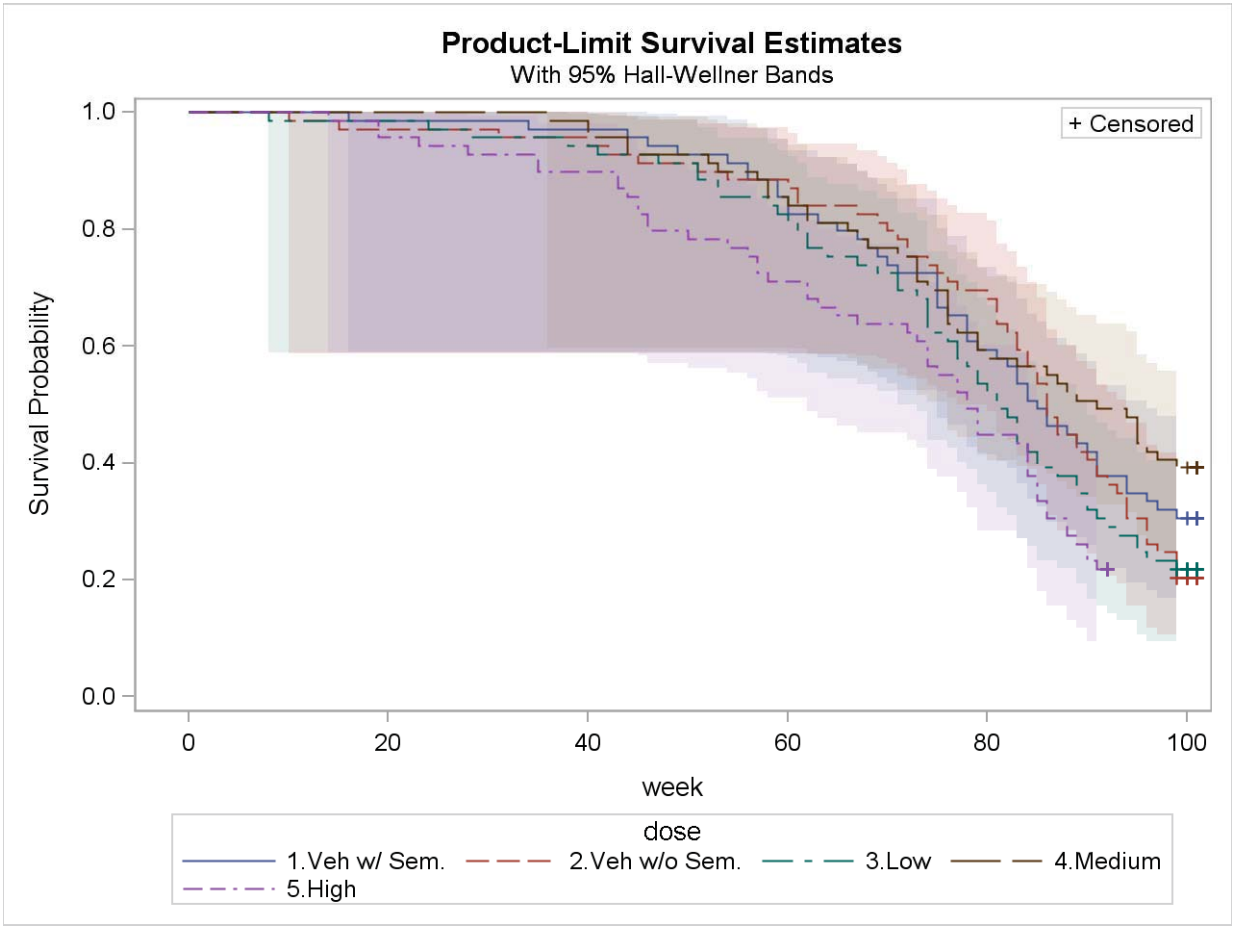
From Figure A.1.1, in male rats, there is a clear association of the high dose group with decreasing survival over time relative to the other dose groups. The other dose groups are more closely intertwined. This is consistent with the results of the tests above. For example, each of the tests of homogeneity over all five dose groups were both statistically significant (logrank p=0.0077, Wilcoxon p= 0.0151), while the test of homogeneity deleting the high dose group was not significant at the usual 0.05 level (logrank p=0.1430, Wilcoxon p= 0.2981). This difference seems to be the primary factor in the tests of trend over groups 3-5 with each vehicle separately treated as the baseline zero (logrank p=0.0258, Wilcoxon p= 0.0228 and logrank p=0.0379, Wilcoxon p= 0.0205, respectively). Further, the tests comparing the high dose to each vehicle were all statistically significant (logrank p=0.0234, Wilcoxon p= 0.0201 and logrank p=0.0179, Wilcoxon p= 0.011, respectively), again consistent with the overall lack of homogenenity in survival. Finally there is no evidence of differences in survival between the vehicle groups (logrank p=0.5192, Wilcoxon p= 0.9104).



Reference ID: 3063799

In female rats results are a bit more complicated. From Figure A.1.2 there still seems to be an association of the high dose group with decreasing survival but the corresponding tests of were statistically significant (logrank p=0.3244, Wilcoxon p= 0.0994). Again, there is no particular evidence of lack of homogeneity in dose groups 1-4 (logrank p=0.8583, Wilcoxon p= 0.7720). On the other hand, the difference between the high dose group and the remaining dose groups does seem to explain most of the statistically significant or close to significant results in the more powerful tests of dose related trend (Group 1 baseline: (logrank p=0.0789, Wilcoxon p= 0.0435, Group 2: logrank p=0.0380, Wilcoxon p= 0.0095). As with male rats, there is no evidence of differences in survival between the vehicle groups (logrank p=0.7496, Wilcoxon p= 0.5242).

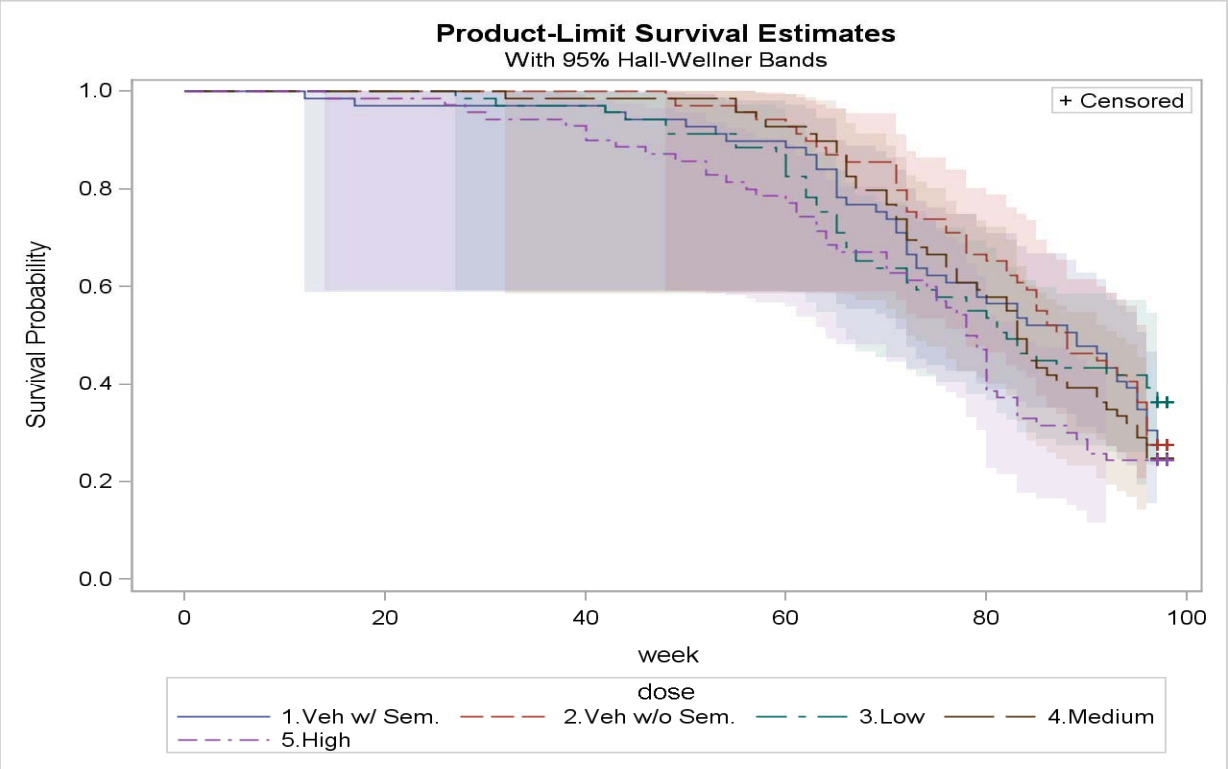
**Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats**






Reference ID: 3063799

**Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats**




Results for mice are presented below:

**Table A.1.2. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study**

| Hypothesis Tested | Males | | Females | |
|---|---|---|---|---|
| | Log rank | Wilcoxon | Log rank | Wilcoxon |
| Rat Homogeneity over Groups 1-5 | 0.6135 | 0.4767 | 0.6251 | 0.6112 |
| No trend over Groups 1, 3-5 | 0.4572 | 0.5423 | 0.8657 | 0.9095 |
| No trend over Groups 2-5 | 0.2062 | 0.1910 | 0.4682 | 0.4259 |
| No Difference Between Groups 1 vs 5 | 0.4384 | 0.4788 | 0.7891 | 0.8593 |
| No Difference Between Groups 2 vs 5 | 0.1140 | 0.0754 | 0.2057 | 0.2453 |
| No Difference Between Groups 1 vs 2 | 0.4525 | 0.3100 | 0.1309 | 0.2324 |

Figures A.1.3 through A.1.4, below, provide similar survival curves for each mouse gender. In both mouse genders the mouse survival curves are generally intertwined. In male mice the vehicle group 2 has the highest survival, generally higher than the high dose group. This seems to explain the close to statistically significant pairwise test between groups 2 and 5 (logrank p=0.1140, Wilcoxon p= 0.0754). No other tests in male mice were close to statistical significance (all $p \geq 0.1940$). In female mice, no tests of homogeneity, trend, or differences were statistically significant (all $p \geq 0.1309$).



Reference ID: 3063799

**Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice**

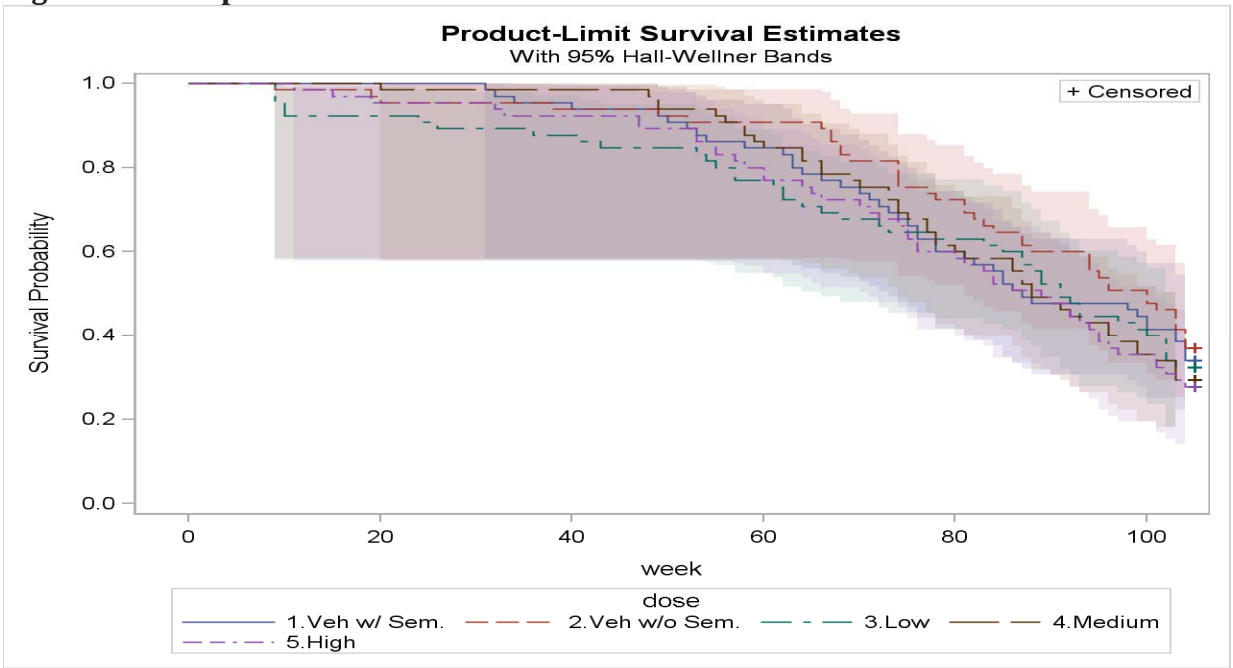
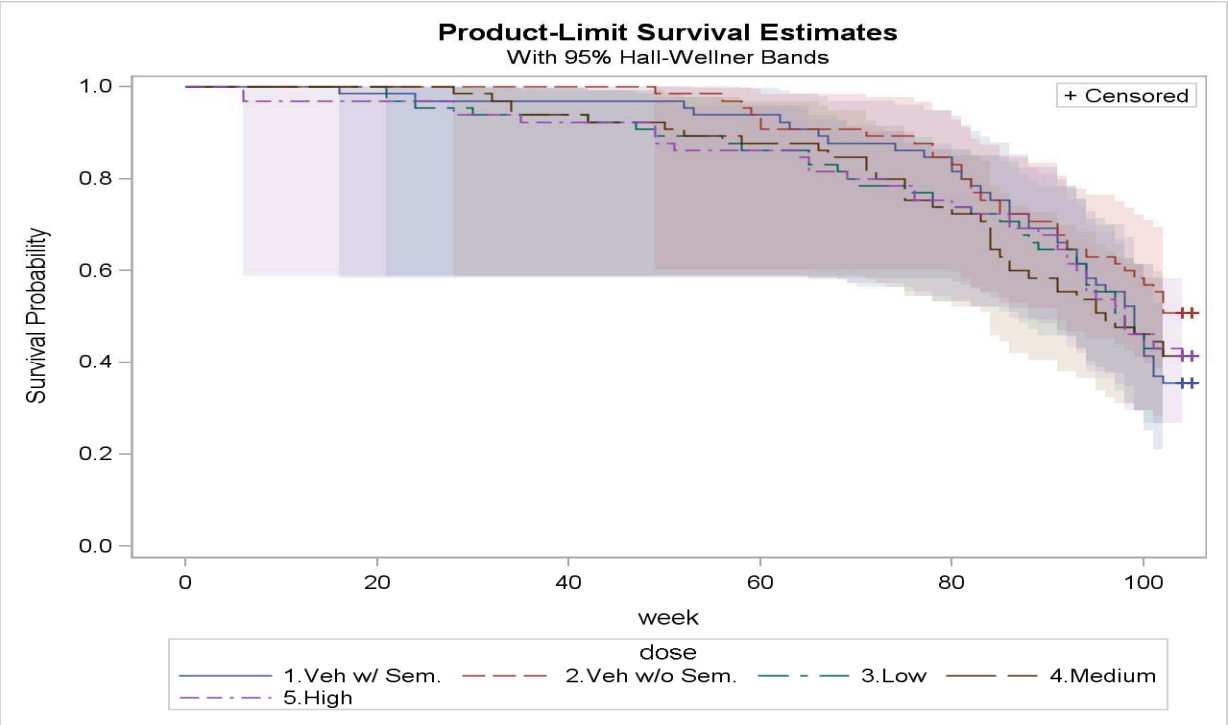



**Figure A.1.4 Kaplan-Meier Survival Curves for Female Mice**






Reference ID: 3063799

**Appendix 2. FDA Poly-k Tumorigenicity Analysis**

The poly-k test, here with k=3, modifies the original Cochran-Armitage test to adjust for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). The tests used here are small sample exact permutation tests of tumor incidence. These do assume all marginal totals are fixed, a debatable assumption. This assumption implies that in the pairwise tests when one dose group has no tumors of the specific type and the other does, there is only one permutation of this pattern. Since that means that the only permutation of the data is the one observed, that means that all possible permutations are as extreme as the pattern observed, and thus the significance level of the observed pattern can be logically expressed as 1.0. One could use the same sort of argument when there were no tumors of the specific type being analyzed in either column of the 2x2 table corresponding to a pairwise comparison. Then an argument could be made that the p-value for this test should also be 1.0. However, largely for readability, in the tables below these p-values are considered as missing (i.e., corresponding to a null test), denoted by a period ".". Note that StatXact adjusts for the variance, which would be 0. Then the significance levels of the test statistics are based on the result of a division by 0, i.e., undefined, and hence StatXact codes these p-values as missing.

The study included two possible control groups, a vehicle group with simethicone (sometimes denoted "V1") and a vehicle group without simethicone (sometimes denoted "V2"). After discussion with the toxicologist the latter group was used as a baseline for tests, so that tests reflect the addition of the active components to the placebo. Incidence in this vehicle group without simethicone is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common.

For each species by gender by organ the number of animals analyzed and used in the statistical tests is presented first. Note that indicating an organ was not examined requires a specification in the data. The tumor incidence for each organ is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, medium, low, and vehicle with simethicone dose groups (group 1) with the vehicle without simethicone (group 2). These statistical tests are conditioned on the animals actually evaluated, ignoring those not analyzed. When animals are selected for evaluation on the basis of criteris related to the endpoint, the assumptions for the computation of the p-values may not hold.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman rules discussed in Section 1.3.1.4 are often applied. That is, when testing for trend over dose and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. As also discussed in section 1.3.1.4, using these adjustments for other tests, like the pairwise tests for the differences between the vehicle without simethicone and the vehicle with simethicone, and the low and medium dose groups can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.



Reference ID: 3063799

Table A.2.1 in rats and Table A.2.2 in mice shows the tumors that had at least one mortality adjusted test whose nominal statistical significance was at least 0.05. Note that when one adjusts for multiplicity these nominally significant comparisons may not be statistically significant. Tables A.2.3 and A.2.4 display all incidences and statistical test results for male and female rats, respectively, while Tables A.2.5 and A.2.6 present similar results in male and female mice. The p-values of the poly-k test are based on exact tests from StatXact as discussed above. As also noted above, the period '.' denotes the p-values of tests of dose groups with no tumors in any group.

**Table A.2.1 Potentially Statistically Significant Neoplasms in Female Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Female | | | | | | | | | | |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| Islet Cell Adenoma/Carcinoma | 2 | 1 | 6 | 1 | 0 | .9580 | 1 | .7305 | .0401 | .8906 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0464 | .1923 | .4839 | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 66 | 69 | | | | | |
| C-CELL ADENOMA | 4 | 1 | 1 | 0 | 4 | .0254 | .1275 | 1 | .7301 | .9752 |

First note that no tests in male rats even achieved the usual frequentist 0.05 significance level. In female rats, using the incidence in the vehicle without simethicone group to specify whether a tumor is treated as common or rare (i.e., more or less than 1%), following the Haseman-Lin rules cited above, none of the comparisons above would be described as statistically significant. That is, in islet cell adenoma in the pancreas comparing the low dose to vehicle we fnd $p = 0.0401 > 0.01$. Results for tests of trend are similar. That is, for systemic pooled hemangioma and hemangiosarcoma the $p = 0.0464 > 0.025$, while for c-cell adenoma of the thyroid $p = 0.0254 > 0.005$.

In mice, results are similar. Again, those organ-tumor combinations with at least one nominally statistically significant result ( $p \leq 0.05$) in mice are summarized below:



Reference ID: 3063799

**Table A.2.2 Potentially Statistically Significant Neoplasms in Mice**

Mice Significant Results

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Male | | | | | | | | | | |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0405 | .2468 | 1 | 1 | .7815 |
| Female | | | | | | | | | | |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| MALIGNANT LYMPHOMA | 14 | 7 | 10 | 17 | 11 | .2266 | .1648 | .0127 | .2514 | .9693 |

Again, adjusting for multiplicity, the test of trend in benign interstitial cell tumor in male mice was not significant ($p = 0.0405 > 0.005$). In female mice the test comparing the medium dose group to the vehicle without simethicone was also not significant, though close (i.e. $p = 0.0127 > 0.01$). Further, as discussed previously, including such tests will inflates type I error level to some value greater than 10%, possibly considerably above 10%. No other comparisons met the multiplicity/rarity adjusted test significance levels.

A complete table in male rats is presented below:

**Table A.2.3 Incidence and Significance Levels of all Tests on Neoplasms in Male Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CORTEX: ADENOMA | 2 | 2 | 1 | 0 | 0 | .9810 | 1 | 1 | .8613 | .6918 |
| CORTEX: CARCINOMA | 0 | 1 | 0 | 1 | 0 | .7361 | 1 | .7635 | 1 | .5000 |
| Cortex: Adenoma/Carcinoma | 2 | 3 | 1 | 1 | 0 | .9631 | 1 | .9467 | .9298 | .5000 |
| MEDULLA BENIGN PHEOCHROMOCYTOMA | 3 | 7 | 2 | 4 | 2 | .8459 | .9570 | .9077 | .9770 | .1667 |
| MEDULLA: MALIGNANT PHEOCHROMOCY | 0 | 1 | 1 | 0 | 0 | .9268 | 1 | 1 | .7227 | .5000 |
| Medulla Pheochromocytoma[B&M] | 3 | 8 | 3 | 4 | 2 | .9167 | .9748 | .9449 | .9613 | .1054 |
| BONE (OTHER) | | | | | | | | | | |
| # Evaluated | 0 | 3 | 2 | 0 | 1 | | | | | |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | .3333 | . | . | .3333 | . |
| BRAIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ASTROCYTOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| BENIGN MENINGIOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| COLON | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| LIPOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| EAR(S) | | | | | | | | | | |
| # Evaluated | 2 | 0 | 3 | 1 | 0 | | | | | |
| FIBROSARCOMA | 0 | 0 | 2 | 0 | 0 | 1 | . | . | . | . |
| MELANOMA, AMELANOTIC | 1 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| SQUAMOUS CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | . |
| JEJUNUM | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOCARCINOMA | 0 | 1 | 1 | 0 | 0 | .9277 | 1 | 1 | .7291 | .5000 |



Reference ID: 3063799

**Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| LIPOMA | 0 | 0 | 1 | 0 | 0 | .7289 | . | . | .4767 | . |
| TUBULAR CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2000 | .4231 | . | . | . |
| LIVER | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CHOLANGIOCARCINOMA | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7528 |
| HEPATOCELLULAR ADENOMA | 2 | 1 | 0 | 1 | 2 | .1189 | .3869 | .7581 | 1 | .8832 |
| HEPATOCELLULAR CARCINOMA | 0 | 2 | 1 | 2 | 0 | .8531 | 1 | .7080 | .8613 | .2472 |
| Hepato. Adenoma/Carcinoma | 2 | 3 | 1 | 3 | 2 | .4264 | .7122 | .6718 | .9267 | .5105 |
| LUMBAR SC | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| SCHWANOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| BRONCHIOLO/ALVEOLAR ADENOMA | 0 | 0 | 1 | 0 | 0 | .7273 | . | . | .4706 | . |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| HISTIOCYTIC SARCOMA | 0 | 1 | 1 | 1 | 0 | .8023 | 1 | .7635 | .7227 | .5000 |
| MALIGNANT LYMPHOMA | 2 | 0 | 1 | 2 | 0 | .5689 | . | .2582 | .4767 | 1 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 55 | 53 | 58 | 59 | 51 | | | | | |
| FIBROADENOMA | 0 | 0 | 0 | 0 | 1 | .1694 | .3889 | . | . | . |
| MEDIASTINAL TISS | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| BENIGN HIBERNOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| MESENTERIC LN | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 68 | 68 | | | | | |
| CARCINOID | 0 | 0 | 0 | 0 | 1 | .2025 | .4286 | . | . | . |
| MESENTERY/PERITO | | | | | | | | | | |
| # Evaluated | 3 | 2 | 3 | 1 | 0 | | | | | |
| MESOTHELIOMA | 1 | 0 | 1 | 0 | 0 | .6667 | . | . | .6667 | 1 |
| PALATE | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 0 | 1 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | 1 | . | . | . | . |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 68 | 69 | | | | | |
| ADENOMA, EXOCRINE | 2 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| ISLET CELL ADENOMA | 4 | 2 | 3 | 2 | 1 | .7146 | .8135 | .7000 | .4554 | .8986 |
| ISLET CELL CARCINOMA | 6 | 2 | 1 | 3 | 0 | .8175 | 1 | .5000 | .8517 | .9729 |
| Islet Cell Adenoma/Carcinoma | 10 | 4 | 4 | 5 | 1 | .8511 | .9392 | .5000 | .5765 | .9825 |
| PARATHYROID | | | | | | | | | | |
| # Evaluated | 54 | 60 | 60 | 58 | 61 | | | | | |
| ADENOMA | 0 | 0 | 1 | 1 | 0 | .5771 | . | .5062 | .4667 | . |



Reference ID: 3063799

**Table A.2.3 (cont/) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| PITUITARY | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOMA, PARS DISTALIS | 33 | 37 | 40 | 37 | 20 | .9808 | .9644 | .5777 | .2943 | .3224 |
| Any Adenoma/Carcinoma | 36 | 38 | 40 | 37 | 20 | .9863 | .9764 | .6534 | .3657 | .4223 |
| PARS DISTALIS: CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| PARS INTERMEDIA: ADENOMA | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .8832 |
| PREPUT/CLIT GL | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| ADENOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| PROSTATE | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CARCINOMA | 1 | 0 | 0 | 1 | 0 | .4848 | . | .5109 | . | 1 |
| HISTIOCYTOMA, FIBROUS | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5000 |
| PAPILLOMA, URETHRA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| SALIVARY GLAND | | | | | | | | | | |
| # Evaluated | 68 | 69 | 69 | 69 | 69 | | | | | |
| HISTIOCYTOMA, FIBROUS | 0 | 0 | 1 | 0 | 0 | .7289 | . | . | .4767 | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOCARCINOMA, MAMMARY | 0 | 0 | 1 | 0 | 0 | .7273 | . | . | .4706 | . |
| BENIGN BASAL CELL TUMOR | 0 | 0 | 0 | 1 | 0 | .4848 | . | .5109 | . | . |
| FIBROADENOMA, MAMMARY | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5000 |
| FIBROMA | 1 | 3 | 0 | 1 | 1 | .6520 | .8914 | .9441 | 1 | .3166 |
| FIBROSARCOMA | 3 | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .8195 |
| KERATOACANTHOMA | 1 | 2 | 0 | 1 | 1 | .4975 | .8080 | .8830 | 1 | .5083 |
| LIPOMA | 2 | 0 | 0 | 2 | 0 | .4414 | . | .2637 | . | 1 |
| MELANOMA, AMELANOTIC | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5055 |
| SARCOMA, NOS | 0 | 0 | 1 | 0 | 0 | .7289 | . | . | .4767 | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2048 | .4304 | . | . | . |
| SQUAMOUS CELL PAPILLOMA | 2 | 0 | 0 | 1 | 0 | .4848 | . | .5109 | . | 1 |
| Sarcomas/Fibroadenoma | 3 | 3 | 1 | 0 | 0 | .9948 | 1 | 1 | .9267 | .6616 |
| Sq.Cell Pap./Carc.+Kerato. | 3 | 2 | 0 | 2 | 2 | .2236 | .5705 | .6998 | 1 | .8263 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| HEMANGIOMA | 0 | 1 | 2 | 2 | 1 | .5081 | .6725 | .5082 | .4564 | .5055 |
| HEMANGIOSARCOMA | 0 | 0 | 2 | 0 | 0 | .7930 | . | . | .2244 | . |
| Hemangioma/Hemangiosarcoma | 0 | 1 | 4 | 2 | 1 | .6717 | .6725 | .5082 | .1531 | .5055 |
| TAIL | | | | | | | | | | |
| # Evaluated | 14 | 15 | 10 | 13 | 8 | | | | | |
| FIBROMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5455 |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 1 | 0 | .4706 | . | .5000 | . | . |
| TESTES | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7528 |
| THYMUS | | | | | | | | | | |
| # Evaluated | 69 | 66 | 68 | 69 | 67 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 0 | 1 | 0 | .4877 | . | .5222 | . | . |
| MALIGNANT THYMOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |



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**Table A.2.3 (cont/) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| THYROID | | | | | | | | | | |
| # Evaluated | 69 | 68 | 69 | 68 | 69 | | | | | |
| C-CELL ADENOMA | 1 | 4 | 3 | 2 | 1 | .8815 | .9421 | .9035 | .7317 | .1804 |
| C-CELL CARCINOMA | 1 | 0 | 1 | 4 | 0 | .5297 | . | .0638 | .4706 | 1 |
| C-Cell Adenoma/Carcinoma | 2 | 4 | 4 | 6 | 1 | .8468 | .9421 | .4120 | .5750 | .3383 |
| FOLLICULAR CELL ADENOMA | 2 | 0 | 2 | 0 | 1 | .3611 | .4231 | . | .2302 | 1 |
| FOLLICULAR CELL CARCINOMA | 2 | 0 | 0 | 3 | 1 | .1870 | .4304 | .1250 | . | 1 |
| Foll. Cell Adenoma/Carcinoma | 4 | 0 | 2 | 3 | 2 | .1603 | .1821 | .1250 | .2302 | 1 |
| URETHRA | | | | | | | | | | |
| # Evaluated | 1 | 1 | 0 | 1 | 1 | | | | | |
| PAPILLOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | . |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 0 | 0 | 2 | 0 | 0 | | | | | |
| CARCINOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |

A complete table in female rats is presented below:

**Table A.2.4 Incidence and Significance Levels of all Tests on Neoplasms in Female Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | | | | |
| # Evaluated | 6 | 1 | 2 | 6 | 2 | | | | | |
| ADENOCARCINOMA, MAMMARY | 2 | 0 | 0 | 0 | 0 | . | . | . | . | . |
| BENIGN HIBERNOMA | 0 | 0 | 0 | 0 | 1 | .2500 | . | . | . | . |
| FIBROADENOMA | 2 | 0 | 0 | 0 | 0 | . | . | . | . | . |
| ADRENALS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| CORTEX: ADENOMA | 0 | 0 | 1 | 1 | 0 | .5767 | . | .4783 | .4783 | . |
| CORTEX: CARCINOMA | 1 | 0 | 1 | 0 | 0 | .7209 | . | . | .4725 | 1 |
| Cortex: Adenoma/Carcinoma | 1 | 0 | 2 | 1 | 0 | .6838 | . | .4783 | .2260 | 1 |
| MEDULLA BENIGN PHEOCHROMOCYTOMA | 0 | 2 | 1 | 0 | 0 | .9783 | 1 | 1 | .8533 | .2690 |
| BICEPS FEMORIS | | | | | | | | | | |
| # Evaluated | 68 | 69 | 69 | 69 | 70 | | | | | |
| HISTIOCYTOMA, FIBROUS | 0 | 0 | 1 | 0 | 0 | .7209 | . | . | .4725 | . |
| BONE (OTHER) | | | | | | | | | | |
| # Evaluated | 1 | 0 | 0 | 1 | 1 | | | | | |
| OSTEOSARCOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | . |
| BRAIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| OLIGODENDROGLIOMA | 0 | 0 | 2 | 0 | 0 | .7822 | . | . | .2260 | . |
| EAR(S) | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 1 | 2 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | . | . | . |



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**Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats**

| Organ Tumor | Veh1 w/s | Veh2 wo/s | Low | Med | Hi | trend | High vs V2 | Med vs V2 | Low vs V2 | Veh 1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| TUBULAR CARCINOMA | 1 | 0 | 0 | 0 | 1 | .2151 | .4353 | . | . | 1 |
| LIVER | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| CHOLANGIOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5161 |
| HEPATOCELLULAR ADENOMA | 1 | 1 | 0 | 1 | 1 | .3370 | .6840 | .7305 | 1 | .7686 |
| HEPATOCELLULAR CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2197 | .4419 | . | . | . |
| Hepato. Adenoma/Carcinoma | 1 | 1 | 0 | 1 | 2 | .1302 | .4122 | .7305 | 1 | .7686 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| BRONCHIOLO/ALVEOLAR CARCINOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5213 |
| SQUAMOUS CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| HISTIOCYTIC SARCOMA | 2 | 0 | 1 | 0 | 1 | .2695 | .4419 | . | .4725 | 1 |
| MALIGNANT LYMPHOMA | 2 | 2 | 2 | 0 | 0 | .9734 | 1 | 1 | .6489 | .7076 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 68 | 64 | 67 | 68 | 70 | | | | | |
| ADENOMA | 0 | 0 | 1 | 1 | 1 | .2710 | .4691 | .5057 | .4881 | . |
| Adenoma/Carcinoma | 1 | 2 | 3 | 1 | 3 | .3359 | .4422 | .8793 | .4661 | .4915 |
| CARCINOMA | 1 | 2 | 3 | 0 | 2 | .5538 | .6346 | 1 | .4661 | .4915 |
| FIBROADENOMA | 5 | 4 | 4 | 4 | 2 | .7918 | .8754 | .6688 | .6302 | .7227 |
| MEDIASTINAL TISS | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 0 | 0 | | | | | |
| BENIGN HIBERNOMA | 0 | 1 | 0 | 0 | 0 | 1 | . | . | . | . |
| MENINGES | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 1 | 0 | | | | | |
| GRANULAR CELL TUMOR | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| MESENTERY/PERITO | | | | | | | | | | |
| # Evaluated | 1 | 2 | 2 | 1 | 1 | | | | | |
| MESOTHELIOMA | 0 | 0 | 0 | 0 | 1 | .3333 | .5000 | . | . | . |
| MUSCLE (OTHER) | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 2 | 1 | | | | | |
| FIBROMA | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| OVARIES | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| BENIGN GRANULOSA CELL TUMOR | 2 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| LUTEOMA | 0 | 0 | 0 | 0 | 1 | .2151 | .4353 | . | . | . |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 2 | 0 | 0 | .7829 | . | . | .2205 | 1 |
| ISLET CELL CARCINOMA | 1 | 1 | 4 | 1 | 0 | .9212 | 1 | .7305 | .1481 | .7686 |
| Islet Cell Adenoma/Carcinoma | 2 | 1 | 6 | 1 | 0 | .9580 | 1 | .7305 | .0401 | .8906 |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOMA, PARS DISTALIS | 60 | 63 | 58 | 57 | 36 | 1 | 1 | .9570 | .9250 | .7973 |
| PARS DISTALIS: CARCINOMA | 2 | 2 | 2 | 0 | 0 | .9723 | 1 | 1 | .6498 | .7151 |



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**Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats**

| Organ Tumor | Veh1 w/s | Veh2 wo/s | Low | Med | Hi | trend | High vs V2 | Med vs V2 | Low vs V2 | Veh 1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| PREPUT/CLIT GL | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| ADENOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOCARCINOMA, MAMMARY | 20 | 23 | 20 | 14 | 6 | .9992 | .9990 | .9549 | .6466 | .3763 |
| ADENOCARCINOMA, MUCINOUS | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| ADENOCARCINOMA, NOS | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| ADENOMA, MAMMARY | 1 | 1 | 3 | 1 | 0 | .8882 | 1 | .7363 | .2761 | .7686 |
| BENIGN BASAL CELL TUMOR | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| FIBROADENOMA, MAMMARY | 20 | 28 | 23 | 33 | 13 | .9852 | .9929 | .3276 | .7860 | .0967 |
| FIBROMA | 1 | 1 | 0 | 3 | 0 | .6439 | 1 | .2843 | 1 | .7686 |
| FIBROSARCOMA | 2 | 0 | 2 | 1 | 1 | .3567 | .4419 | .4783 | .2205 | 1 |
| HISTIOCYTOMA, FIBROUS | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7735 |
| KERATOACANTHOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5161 |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | .7209 | . | . | .4725 | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 1 | 0 | .4740 | . | .4839 | . | . |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | .2151 | .4353 | . | . | . |
| Sq.Cell Pap./Carc.+Kerato. | 0 | 1 | 0 | 1 | 1 | .3378 | .6840 | .7363 | 1 | .5161 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| HEMANGIOMA | 0 | 0 | 0 | 0 | 1 | .2151 | .4353 | . | . | . |
| HEMANGIOSARCOMA | 0 | 0 | 0 | 1 | 1 | .1603 | .4419 | .4839 | . | . |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0464 | .1923 | .4839 | . | . |
| TAIL | | | | | | | | | | |
| # Evaluated | 9 | 11 | 7 | 11 | 3 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 1 | 0 | .4444 | . | .5263 | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 66 | 69 | | | | | |
| C-CELL ADENOMA | 4 | 1 | 1 | 0 | 4 | .0254 | .1275 | 1 | .7301 | .9752 |
| C-CELL CARCINOMA | 1 | 1 | 3 | 0 | 0 | .9435 | 1 | 1 | .2753 | .7690 |
| C-Cell Adenoma/Carcinoma | 5 | 2 | 4 | 0 | 4 | .2088 | .2536 | 1 | .3073 | .9511 |
| FOLLICULAR CELL ADENOMA | 0 | 1 | 1 | 0 | 1 | .4859 | .6840 | 1 | .7245 | .5217 |
| FOLLICULAR CELL CARCINOMA | 1 | 0 | 0 | 2 | 1 | .1614 | .4405 | .2199 | . | 1 |
| Foll. Cell Adenoma/Carcinoma | 1 | 1 | 1 | 2 | 2 | .1996 | .4023 | .4495 | .7245 | .7740 |
| UTERUS W/ CERVIX | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ENDOMETRIAL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2151 | .4353 | . | . | . |
| ENDOMETRIAL STROMAL POLYP | 4 | 2 | 6 | 2 | 1 | .8628 | .8200 | .6586 | .0955 | .9119 |
| Endo. Carc./Stromal Polyp | 4 | 2 | 6 | 2 | 2 | .6856 | .5792 | .6586 | .0955 | .9119 |
| LEIOMYOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| MALIGNANT SCHWANNOMA | 2 | 1 | 0 | 0 | 2 | .1252 | .4142 | 1 | 1 | .8903 |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 1 | 0 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |



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## Table A.2.5 Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | | | | |
| # Evaluated | 4 | 2 | 2 | 3 | 2 | | | | | |
| LIPOMA | 0 | 1 | 0 | 0 | 0 | 1 | . | 1 | 1 | .3333 |
| ADRENALS | | | | | | | | | | |
| # Evaluated | 62 | 65 | 62 | 65 | 64 | | | | | |
| CORTEX: ADENOMA | 2 | 2 | 5 | 2 | 5 | .1665 | .1455 | .6372 | .1284 | .7518 |
| Alimemtary Canal | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| Adenoma | 0 | 1 | 2 | 0 | 1 | .5892 | .7091 | 1 | .4554 | .5294 |
| DISTAL FEMUR | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| OSTEOMA | 0 | 0 | 0 | 1 | 0 | .4815 | . | .4706 | . | . |
| EYES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| ADENOMA, SEBACEOUS | 0 | 0 | 0 | 1 | 1 | .1712 | .4578 | .4767 | . | . |
| HARDERIAN GL | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 64 | | | | | |
| ADENOMA | 10 | 5 | 9 | 6 | 6 | .4605 | .3649 | .4349 | .1331 | .9682 |
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| TUBULAR ADENOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5294 |
| LIVER | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEPATOCELLULAR ADENOMA | 5 | 8 | 11 | 7 | 6 | .7541 | .7040 | .6444 | .2473 | .3549 |
| HEPATOCELLULAR CARCINOMA | 17 | 15 | 17 | 15 | 18 | .1902 | .1829 | .4752 | .2491 | .8489 |
| Hepato. Adenoma/Carcinoma | 19 | 22 | 25 | 21 | 21 | .5548 | .4740 | .5895 | .2045 | .5172 |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | .7239 | . | . | .4706 | . |
| LUNGS | | | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | 65 | | | | | |
| BRONCHIOLAR/ALVEOLAR ADENOMA/CY | 6 | 9 | 5 | 6 | 4 | .8317 | .9283 | .8005 | .8721 | .3731 |
| BRONCHIOLAR/ALVEOLAR CARCINOMA | 6 | 11 | 6 | 6 | 3 | .9653 | .9888 | .9059 | .8964 | .2219 |
| Bronch. Alv. Adenoma/Carcinoma | 11 | 18 | 10 | 11 | 7 | .9621 | .9887 | .9040 | .9325 | .1978 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| GRANULOCYTIC LEUKEMIA | 0 | 0 | 1 | 1 | 1 | .2657 | .4578 | .4767 | .4643 | . |
| HISTIOCYTIC SARCOMA | 1 | 1 | 1 | 1 | 0 | .8061 | 1 | .7227 | .7160 | .7756 |
| MALIGNANT LYMPHOMA | 7 | 9 | 14 | 7 | 12 | .2996 | .2322 | .7351 | .1254 | .4694 |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 62 | 65 | 63 | 65 | 65 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 63 | 64 | 62 | 64 | 65 | | | | | |
| PARS DISTALIS-ADENOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5301 |
| RECTUM/LOW COLON | | | | | | | | | | |
| # Evaluated | 61 | 65 | 65 | 64 | 62 | | | | | |
| ADENOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5422 |
| SKIN | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| FIBROMA | 0 | 0 | 1 | 0 | 0 | .7222 | . | . | .4643 | . |
| FIBROSARCOMA | 2 | 1 | 1 | 0 | 0 | .9241 | 1 | 1 | .7160 | .8958 |
| SEBACEOUS CELL ADENOMA | 0 | 0 | 1 | 0 | 0 | .7222 | . | . | .4643 | . |



Reference ID: 3063799

## Table A.2.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| STOMACH | | | | | | | | | | |
| # Evaluated | 64 | 64 | 65 | 65 | 65 | | | | | |
| GLANDULAR MUCOSA: ADENOMA | 0 | 0 | 2 | 0 | 1 | .4019 | .4578 | . | .2185 | . |
| Systemic | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEMANGIOMA | 0 | 0 | 0 | 2 | 0 | .4750 | . | .2185 | . | . |
| HEMANGIOSARCOMA | 3 | 3 | 0 | 2 | 2 | .3937 | .7547 | .7732 | 1 | .7153 |
| Hemangioma/Hemangiosarcoma | 3 | 3 | 0 | 4 | 2 | .4137 | .7547 | .4213 | 1 | .7153 |
| MESOTHELIOMA | 0 | 0 | 0 | 1 | 1 | .1712 | .4578 | .4767 | . | . |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0405 | .2468 | 1 | 1 | .7815 |
| THYROID | | | | | | | | | | |
| # Evaluated | 62 | 60 | 62 | 64 | 62 | | | | | |
| FOLLICULAR CELL ADENOMA | 0 | 0 | 0 | 0 | 1 | .2390 | .4691 | . | . | . |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 1 | 0 | 0 | 0 | 0 | | | | | |
| CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | . |

## Table A.2.6 Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 64 | | | | | |
| CORTEX: ADENOMA | 1 | 1 | 1 | 0 | 1 | .5069 | .7144 | 1 | .7204 | .7675 |
| MEDULLA: MALIGNANT PHEOCHROMO-CYTOMA | 0 | 0 | 0 | 1 | 0 | .4837 | . | .4737 | . | . |
| Alimemtary Canal | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| Adenoma/Carcinoma | 0 | 0 | 0 | 1 | 1 | .1797 | .4792 | .4681 | . | . |
| BICEP FEMORIS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| SCHWANNOMA | 0 | 0 | 0 | 1 | 0 | .4865 | . | .4737 | . | . |
| BRAIN | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN MENINGIOMA | 2 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| OLIGODENDROGLIOMA | 0 | 0 | 0 | 1 | 0 | .4837 | . | .4681 | . | . |
| DISTAL FEMUR | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 1 | 0 | .4865 | . | .4737 | . | . |
| GALLBLADDER | | | | | | | | | | |
| # Evaluated | 51 | 59 | 54 | 56 | 53 | | | | | |
| PAPILLOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5412 |
| HARDERIAN GL | | | | | | | | | | |
| # Evaluated | 65 | 65 | 64 | 65 | 65 | | | | | |
| ADENOMA | 5 | 5 | 9 | 9 | 10 | .1426 | .0974 | .1512 | .1409 | .6679 |
| CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |



Reference ID: 3063799

**Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| TUBULAR CARCINOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5102 |
| LIVER | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| CHOLANGIOCARCINOMA | 0 | 0 | 0 | 1 | 0 | .4837 | . | .4681 | . | . |
| HEPATOCELLULAR ADENOMA | 0 | 0 | 2 | 0 | 1 | .4161 | .4737 | . | .2270 | . |
| HEPATOCELLULAR CARCINOMA | 0 | 1 | 1 | 2 | 1 | .4716 | .7204 | .4442 | .7204 | .5152 |
| Hepato. Adenoma/Carcinoma | 0 | 1 | 3 | 2 | 2 | .4162 | .4527 | .4442 | .2705 | .5152 |
| OSTEOSARCOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5102 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BRONCHIOLAR/ALVEOLAR ADENOMA/ CYTOMA 0000000000000 | 5 | 6 | 4 | 2 | 3 | .7797 | .8877 | .9561 | .7754 | .5423 |
| BRONCHIOLAR/ALVEOLAR CARCINOMA | 3 | 3 | 0 | 1 | 1 | .6959 | .9248 | .9215 | 1 | .6801 |
| Bronch. Alv. Adenoma/Carcinoma | 7 | 9 | 4 | 3 | 4 | .8175 | .9373 | .9741 | .9321 | .4432 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| GRANULOCYTIC LEUKEMIA | 1 | 0 | 0 | 0 | 1 | .2486 | .4792 | . | . | 1 |
| HISTIOCYTIC SARCOMA | 2 | 7 | 4 | 3 | 4 | .7038 | .8653 | .9312 | .8653 | .1003 |
| MALIGNANT LYMPHOMA | 14 | 7 | 10 | 17 | 11 | .2266 | .1648 | .0127 | .2514 | .9693 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 56 | 59 | 60 | 61 | 60 | | | | | |
| ADENOCARCINOMA | 0 | 2 | 1 | 0 | 1 | .6554 | .8522 | 1 | .8522 | .2824 |
| MESENTERIC LN | | | | | | | | | | |
| # Evaluated | 60 | 60 | 54 | 59 | 61 | | | | | |
| OSTEOSARCOMA | 0 | 0 | 0 | 0 | 1 | .2616 | .4891 | . | . | . |
| OVARIES | | | | | | | | | | |
| # Evaluated | 64 | 65 | 64 | 65 | 65 | | | | | |
| BENIGN GRANULOSA CELL TUMOR | 2 | 1 | 1 | 1 | 0 | .8117 | 1 | .7197 | .7256 | .8900 |
| CYSTADENOMA/ADENOMA, OVARY OR O | 0 | 0 | 1 | 3 | 0 | .6898 | . | .1025 | .4792 | . |
| LUTEOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| MALIGNANT GRANULOSA CELL TUMOR | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| SERTOLI CELL TUMOR | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 65 | 64 | 64 | 64 | 64 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 63 | 64 | | | | | |
| PARS DISTALIS-ADENOMA | 3 | 0 | 2 | 0 | 1 | .4178 | .4737 | . | .2217 | 1 |
| PSOAS MUSCLE | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 1 | 0 | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | 65 | | | | | |
| FIBROSARCOMA | 1 | 2 | 0 | 0 | 1 | .5735 | .8626 | 1 | 1 | .5078 |
| MAST CELL TUMOR | 0 | 0 | 0 | 0 | 1 | .2500 | .4842 | . | . | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2459 | .4787 | . | . | . |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | .2459 | .4787 | . | . | . |



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**Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V2 | Med vs V2 | Low vs V2 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| STOMACH | | | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 64 | 65 | | | | | |
| FORESTOMACH: SQUAMOUS CELL CARC | 0 | 0 | 0 | 1 | 0 | .4837 | . | .4681 | . | . |
| GLANDULAR MUCOSA: ADENOMA | 0 | 0 | 0 | 0 | 1 | .2486 | .4792 | . | . | . |
| Systemic | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEMANGIOMA | 2 | 2 | 4 | 6 | 4 | .3275 | .3006 | .1033 | .2908 | .7140 |
| HEMANGIOSARCOMA | 4 | 5 | 2 | 2 | 0 | .9891 | 1 | .9223 | .9265 | .5257 |
| Hemangioma/Hemangiosarcoma | 6 | 6 | 6 | 8 | 4 | .7483 | .7964 | .3107 | .5465 | .6617 |
| TAIL | | | | | | | | | | |
| # Evaluated | 5 | 0 | 0 | 0 | 1 | | | | | |
| CHORDOMA | 0 | 0 | 0 | 0 | 1 | 1 | . | . | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 65 | 62 | 62 | 64 | 63 | | | | | |
| C-CELL ADENOMA | 0 | 0 | 0 | 0 | 1 | .2444 | .4731 | . | . | . |
| FOLLICULAR CELL ADENOMA | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .5052 |
| UTERUS W/ CERVIX | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN GRANULAR CELL TUMOR | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| ENDOMETRIAL CARCINOMA | 1 | 0 | 0 | 0 | 0 | . | . | . | . | 1 |
| ENDOMETRIAL STROMAL POLYP | 4 | 7 | 6 | 7 | 6 | .5332 | .6397 | .5166 | .6240 | .3230 |
| ENDOMETRIAL STROMAL SARCOMA | 2 | 0 | 1 | 1 | 0 | .6041 | . | .4681 | .4737 | 1 |
| Endo. Stromal Adenoma/Sarcoma | 6 | 7 | 7 | 8 | 6 | .5903 | .6397 | .3993 | .4991 | .5610 |
| LEIOMYOMA | 0 | 3 | 3 | 1 | 1 | .8595 | .9248 | .9215 | .6107 | .1328 |
| LEIOMYOSARCOMA | 4 | 4 | 1 | 3 | 0 | .9554 | 1 | .7272 | .9616 | .6648 |
| Leiomyoma/Leiomysarcoma | 4 | 7 | 4 | 4 | 1 | .9792 | .9952 | .8563 | .8648 | .2860 |
| VAGINA | | | | | | | | | | |
| # Evaluated | 64 | 64 | 62 | 65 | 64 | | | | | |
| ADENOMA | 0 | 0 | 0 | 1 | 1 | .1810 | .4787 | .4787 | . | . |
| LEIOMYOMA | 0 | 0 | 0 | 0 | 1 | .2473 | .4787 | . | . | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2473 | .4787 | . | . | . |



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## Appendix 3. Alternative FDA Poly-k Tumorigenicity Analysis

The only difference between this analysis and the analysis in the previous appendix is the role of the vehicle with simethicone, i.e. vehicle 1. In Appendix 3, except for a comparison with vehicle group 2 this is largely ignored. In the alternative analysis presented here tests of trend use this group 1 as the baseline and comparator group. A discussion of why this may be a preferable analysis is given in Section 1.3.1.1. Other comments in appendix 3 apply to this analysis as well.

Table A.3.1 below shows the tumors in both rats and mice that had at least one mortality adjusted test whose nominal statistical significance was at least 0.05.

**Table A.3.1 Potentially Statistically Significant Neoplasms in Rats and Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh1 vs V2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Female Rats | | | | | | | | | | |
| SKIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| FIBROADENOMA, MAMMARY | 20 | 28 | 23 | 33 | 13 | .8750 | .8504 | .0250 | .2480 | .0967 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0489 | .2066 | .5000 | . | . |
| Male Mice | | | | | | | | | | |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0442 | .2883 | 1 | 1 | .7815 |

As before, no tests in male rats even achieved the usual frequentist 0.05 significance level. In female rats, using the incidence in the vehicle without simethicone group to specify whether a tumor is treated as common or rare (i.e., more or less than 1%), following the Haseman-Lin adjustment for multiplicity cited above, the test of trend in systemic pooled hemangioma and hemangiosarcoma was not statistically significant ($p = 0.0489 > 0.025$). Even adjusting for the inflation in type I error for including such tests, the comparison between the medium dose group and vehicle 1 would also not be classified as statistically significant ($p = 0.0250 > 0.01$). Similarly, in male mice, the test of trend in benign interstitial cell tumor was also not statistically significant ( $p – 0.0442 > 0.005$).

Again complete incidence tables and the significance levels of tests of trend and pairwise compaisons between dose groups amd the first control are presnetd in Tables A.3.2-A.3.6 below.



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## Table A.3.2 Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CORTEX: ADENOMA | 2 | 2 | 1 | 0 | 0 | .9810 | 1 | 1 | .8613 | .6918 |
| CORTEX: CARCINOMA | 0 | 1 | 0 | 1 | 0 | .4848 | . | .5109 | . | .5000 |
| Cortex: Adenoma/Carcinoma | 2 | 3 | 1 | 1 | 0 | .9119 | 1 | .8870 | .8613 | .5000 |
| MEDULLA BENIGN PHEOCHROMOCYTOMA | 3 | 7 | 2 | 4 | 2 | .4996 | .7210 | .5246 | .7895 | .1667 |
| MEDULLA: MALIGNANT PHEOCHROM. | 0 | 1 | 1 | 0 | 0 | .7273 | . | . | .4706 | .5000 |
| Medulla Pheochromocytoma[B&M] | 3 | 8 | 3 | 4 | 2 | .5693 | .7210 | .5246 | .6163 | .1054 |
| BONE (OTHER) | | | | | | | | | | |
| # Evaluated | 0 | 3 | 2 | 0 | 1 | | | | | |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| BRAIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ASTROCYTOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| BENIGN MENINGIOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| COLON | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| LIPOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| EAR(S) | | | | | | | | | | |
| # Evaluated | 2 | 0 | 3 | 1 | 0 | | | | | |
| FIBROSARCOMA | 0 | 0 | 2 | 0 | 0 | .3333 | . | . | .3333 | . |
| MELANOMA, AMELANOTIC | 1 | 0 | 1 | 0 | 0 | .8333 | . | . | .8333 | . |
| SQUAMOUS CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | . | . | 1 | . |
| JEJUNUM | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOCARCINOMA | 0 | 1 | 1 | 0 | 0 | .7289 | . | . | .4767 | .5000 |
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| LIPOMA | 0 | 0 | 1 | 0 | 0 | .7289 | . | . | .4767 | . |
| TUBULAR CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2000 | .4231 | . | . | . |
| LIVER | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CHOLANGIOCARCINOMA | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7528 |
| HEPATOCELLULAR ADENOMA | 2 | 1 | 0 | 1 | 2 | .2271 | .5797 | .8870 | 1 | .8832 |
| HEPATOCELLULAR CARCINOMA | 0 | 2 | 1 | 2 | 0 | .5689 | . | .2582 | .4767 | .2472 |
| Hepato. Adenoma/Carcinoma | 2 | 3 | 1 | 3 | 2 | .3097 | .5797 | .5208 | .8613 | .5105 |
| LUMBAR SC | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| SCHWANOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| BRONCHIOLO/ALVEOLAR ADENOMA | 0 | 0 | 1 | 0 | 0 | .7273 | . | . | .4706 | . |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| HISTIOCYTIC SARCOMA | 0 | 1 | 1 | 1 | 0 | .5798 | . | .5109 | .4706 | .5000 |
| MALIGNANT LYMPHOMA | 2 | 0 | 1 | 2 | 0 | .8531 | 1 | .7080 | .8613 | 1 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 55 | 53 | 58 | 59 | 51 | | | | | |
| FIBROADENOMA | 0 | 0 | 0 | 0 | 1 | .1694 | .3889 | . | . | . |
| MEDIASTINAL TISS | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| BENIGN HIBERNOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |



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**Table A.3.2 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| MESENTERIC LN | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 68 | 68 | | | | | |
| CARCINOID | 0 | 0 | 0 | 0 | 1 | .2025 | .4286 | . | . | . |
| MESENTERY/PERITO | | | | | | | | | | |
| # Evaluated | 3 | 2 | 3 | 1 | 0 | | | | | |
| MESOTHELIOMA | 1 | 0 | 1 | 0 | 0 | 1 | . | . | 1 | 1 |
| PALATE | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 0 | 1 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | 1 | . | . | . | . |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 68 | 69 | | | | | |
| ADENOMA, EXOCRINE | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| ISLET CELL ADENOMA | 4 | 2 | 3 | 2 | 1 | .8794 | .9421 | .9035 | .7430 | .8986 |
| ISLET CELL CARCINOMA | 6 | 2 | 1 | 3 | 0 | .9853 | 1 | .9263 | .9908 | .9729 |
| Islet Cell Adenoma/Carcinoma | 10 | 4 | 4 | 5 | 1 | .9921 | .9987 | .9603 | .9703 | .9825 |
| PARATHYROID | | | | | | | | | | |
| # Evaluated | 54 | 60 | 60 | 58 | 61 | | | | | |
| ADENOMA | 0 | 0 | 1 | 1 | 0 | .5987 | . | .5325 | .4930 | . |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOMA, PARS DISTALIS | 33 | 37 | 40 | 37 | 20 | .9480 | .8846 | .3224 | .1169 | .3224 |
| Any Adenoma/Carcinoma | 36 | 38 | 40 | 37 | 20 | .9736 | .9480 | .5000 | .2310 | .4223 |
| PARS DISTALIS: CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| PARS INTERMEDIA: ADENOMA | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .8832 |
| PREPUT/CLIT GL | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| ADENOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| PROSTATE | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| CARCINOMA | 1 | 0 | 0 | 1 | 0 | .7361 | 1 | .7635 | 1 | 1 |
| HISTIOCYTOMA, FIBROUS | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5000 |
| PAPILLOMA, URETHRA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| SALIVARY GLAND | | | | | | | | | | |
| # Evaluated | 68 | 69 | 69 | 69 | 69 | | | | | |
| HISTIOCYTOMA, FIBROUS | 0 | 0 | 1 | 0 | 0 | .7333 | . | . | .4824 | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ADENOCARCINOMA, MAMMARY | 0 | 0 | 1 | 0 | 0 | .7273 | . | . | .4706 | . |
| BENIGN BASAL CELL TUMOR | 0 | 0 | 0 | 1 | 0 | .4848 | . | .5109 | . | . |
| FIBROADENOMA, MAMMARY | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5000 |
| FIBROMA | 1 | 3 | 0 | 1 | 1 | .3301 | .6703 | .7635 | 1 | .3166 |
| FIBROSARCOMA | 3 | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .8195 |
| KERATOACANTHOMA | 1 | 2 | 0 | 1 | 1 | .3301 | .6703 | .7635 | 1 | .5083 |
| LIPOMA | 2 | 0 | 0 | 2 | 0 | .7938 | 1 | .7157 | 1 | 1 |
| MELANOMA, AMELANOTIC | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5055 |
| SARCOMA, NOS | 0 | 0 | 1 | 0 | 0 | .7289 | . | . | .4767 | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2048 | .4304 | . | . | . |
| SQUAMOUS CELL PAPILLOMA | 2 | 0 | 0 | 1 | 0 | .8791 | 1 | .8870 | 1 | 1 |
| Sarcomas/Fibroadenoma | 3 | 3 | 1 | 0 | 0 | .9948 | 1 | 1 | .9267 | .6616 |
| Sq.Cell Pap./Carc.+Kerato. | 3 | 2 | 0 | 2 | 2 | .3590 | .7210 | .8328 | 1 | .8263 |



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## Table A.3.2 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| HEMANGIOMA | 0 | 1 | 2 | 2 | 1 | .3510 | .4304 | .2582 | .2244 | .5055 |
| HEMANGIOSARCOMA | 0 | 0 | 2 | 0 | 0 | .7930 | . | . | .2244 | . |
| Hemangioma/Hemangiosarcoma | 0 | 1 | 4 | 2 | 1 | .5514 | .4304 | .2582 | .0503 | .5055 |
| TAIL | | | | | | | | | | |
| # Evaluated | 14 | 15 | 10 | 13 | 8 | | | | | |
| FIBROMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5455 |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 1 | 0 | .5000 | . | .5455 | . | . |
| TESTES | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7528 |
| THYMUS | | | | | | | | | | |
| # Evaluated | 69 | 66 | 68 | 69 | 67 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 0 | 1 | 0 | .4817 | . | .5109 | . | . |
| MALIGNANT THYMOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| THYROID | | | | | | | | | | |
| # Evaluated | 69 | 68 | 69 | 68 | 69 | | | | | |
| C-CELL ADENOMA | 1 | 4 | 3 | 2 | 1 | .5946 | .6703 | .5083 | .2647 | .1804 |
| C-CELL CARCINOMA | 1 | 0 | 1 | 4 | 0 | .6824 | 1 | .1944 | .7227 | 1 |
| C-Cell Adenoma/Carcinoma | 2 | 4 | 4 | 6 | 1 | .6991 | .8135 | .1555 | .2834 | .3383 |
| FOLLICULAR CELL ADENOMA | 2 | 0 | 2 | 0 | 1 | .7080 | .8135 | 1 | .6653 | 1 |
| FOLLICULAR CELL CARCINOMA | 2 | 0 | 0 | 3 | 1 | .4628 | .8206 | .5105 | 1 | 1 |
| Foll. Cell Adenoma/Carcinoma | 4 | 0 | 2 | 3 | 2 | .6196 | .8213 | .7919 | .8823 | 1 |
| URETHRA | | | | | | | | | | |
| # Evaluated | 1 | 1 | 0 | 1 | 1 | | | | | |
| PAPILLOMA | 1 | 0 | 0 | 0 | 0 | 1 | . | . | . | . |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 0 | 0 | 2 | 0 | 0 | | | | | |
| CARCINOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |

## Table A.3.3 Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | | | | |
| # Evaluated | 6 | 1 | 2 | 6 | 2 | | | | | |
| ADENOCARCINOMA, MAMMARY | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | . | . |
| BENIGN HIBERNOMA | 0 | 0 | 0 | 0 | 1 | .1111 | .1667 | . | . | . |
| FIBROADENOMA | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | . | . |
| ADRENALS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| CORTEX: ADENOMA | 0 | 0 | 1 | 1 | 0 | .5896 | . | .4944 | .4944 | . |
| CORTEX: CARCINOMA | 1 | 0 | 1 | 0 | 0 | .9303 | 1 | 1 | .7414 | 1 |
| Cortex: Adenoma/Carcinoma | 1 | 0 | 2 | 1 | 0 | .8516 | 1 | .7472 | .4915 | 1 |
| MEDULLA BENIGN PHEOCHROMOCYTOMA | 0 | 2 | 1 | 0 | 0 | .7337 | . | . | .4886 | .2690 |
| BICEPS FEMORIS | | | | | | | | | | |
| # Evaluated | 68 | 69 | 69 | 69 | 70 | | | | | |
| HISTIOCYTOMA, FIBROUS | 0 | 0 | 1 | 0 | 0 | .7337 | . | . | .4886 | . |
| BONE (OTHER) | | | | | | | | | | |
| # Evaluated | 1 | 0 | 0 | 1 | 1 | | | | | |
| OSTEOSARCOMA | 1 | 0 | 0 | 0 | 0 | 1 | . | . | . | . |



Reference ID: 3063799

**Table A.3.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| OLIGODENDROGLIOMA | 0 | 0 | 2 | 0 | 0 | .7932 | . | . | .2416 | . |
| EAR(S) | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 1 | 2 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| TUBULAR CARCINOMA | 1 | 0 | 0 | 0 | 1 | .3910 | .7019 | 1 | 1 | 1 |
| LIVER | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| CHOLANGIOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5161 |
| HEPATOCELLULAR ADENOMA | 1 | 1 | 0 | 1 | 1 | .3467 | .7019 | .7472 | 1 | .7686 |
| HEPATOCELLULAR CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2235 | .4578 | . | . | . |
| Hepato. Adenoma/Carcinoma | 1 | 1 | 0 | 1 | 2 | .1362 | .4361 | .7472 | 1 | .7686 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| BRONCHIOLO/ALVEOLAR CARCINOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5213 |
| SQUAMOUS CELL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| HISTIOCYTIC SARCOMA | 2 | 0 | 1 | 0 | 1 | .6592 | .8407 | 1 | .8663 | 1 |
| MALIGNANT LYMPHOMA | 2 | 2 | 2 | 0 | 0 | .9757 | 1 | 1 | .6658 | .7076 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 68 | 64 | 67 | 68 | 70 | | | | | |
| ADENOMA | 0 | 0 | 1 | 1 | 1 | .2632 | .4578 | .4944 | .4767 | . |
| Adenoma/Carcinoma | 1 | 2 | 3 | 1 | 3 | .2154 | .2558 | .7472 | .2736 | .4915 |
| CARCINOMA | 1 | 2 | 3 | 0 | 2 | .4032 | .4361 | 1 | .2736 | .4915 |
| FIBROADENOMA | 5 | 4 | 4 | 4 | 2 | .8389 | .9151 | .7464 | .7100 | .7227 |
| MEDIASTINAL TISS | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 0 | 0 | | | | | |
| BENIGN HIBERNOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| MENINGES | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 1 | 0 | | | | | |
| GRANULAR CELL TUMOR | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| MESENTERY/PERITO | | | | | | | | | | |
| # Evaluated | 1 | 2 | 2 | 1 | 1 | | | | | |
| MESOTHELIOMA | 0 | 0 | 0 | 0 | 1 | .3333 | .5000 | . | . | . |
| MUSCLE (OTHER) | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 2 | 1 | | | | | |
| FIBROMA | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| OVARIES | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| BENIGN GRANULOSA CELL TUMOR | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| LUTEOMA | 0 | 0 | 0 | 0 | 1 | .2189 | .4512 | . | . | . |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 69 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 2 | 0 | 0 | .9282 | 1 | 1 | .4828 | 1 |
| ISLET CELL CARCINOMA | 1 | 1 | 4 | 1 | 0 | .9283 | 1 | .7472 | .1663 | .7686 |
| Islet Cell Adenoma/Carcinoma | 2 | 1 | 6 | 1 | 0 | .9820 | 1 | .8750 | .1187 | .8906 |



Reference ID: 3063799

**Table A.3.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| PITUITARY | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOMA, PARS DISTALIS | 60 | 63 | 58 | 57 | 36 | 1 | 1 | .9817 | .9658 | .7973 |
| PARS DISTALIS: CARCINOMA | 2 | 2 | 2 | 0 | 0 | .9758 | 1 | 1 | .6747 | .7151 |
| PREPUT/CLIT GL | | | | | | | | | | |
| # Evaluated | 0 | 0 | 1 | 0 | 0 | | | | | |
| ADENOMA | 0 | 0 | 1 | 0 | 0 | 1 | . | . | . | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ADENOCARCINOMA, MAMMARY | 20 | 23 | 20 | 14 | 6 | .9973 | .9959 | .8835 | .4511 | .3763 |
| ADENOCARCINOMA, MUCINOUS | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| ADENOCARCINOMA, NOS | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| ADENOMA, MAMMARY | 1 | 1 | 3 | 1 | 0 | .8969 | 1 | .7528 | .2997 | .7686 |
| BENIGN BASAL CELL TUMOR | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| FIBROADENOMA, MAMMARY | 20 | 28 | 23 | 33 | 13 | .8750 | .8504 | .0250 | .2480 | .0967 |
| FIBROMA | 1 | 1 | 0 | 3 | 0 | .6551 | 1 | .3082 | 1 | .7686 |
| FIBROSARCOMA | 2 | 0 | 2 | 1 | 1 | .7084 | .8407 | .8708 | .6658 | 1 |
| HISTIOCYTOMA, FIBROUS | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | .7735 |
| KERATOACANTHOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5161 |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | .7337 | . | . | .4886 | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 1 | 0 | .4824 | . | .5000 | . | . |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | .2189 | .4512 | . | . | . |
| Sq.Cell Pap./Carc.+Kerato. | 0 | 1 | 0 | 1 | 1 | .1623 | .4512 | .5000 | . | .5161 |
| Systemic | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| HEMANGIOMA | 0 | 0 | 0 | 0 | 1 | .2189 | .4512 | . | . | . |
| HEMANGIOSARCOMA | 0 | 0 | 0 | 1 | 1 | .1660 | .4578 | .5000 | . | . |
| Hemangioma/Hemangiosarcoma | 0 | 0 | 0 | 1 | 2 | .0489 | .2066 | .5000 | . | . |
| TAIL | | | | | | | | | | |
| # Evaluated | 9 | 11 | 7 | 11 | 3 | | | | | |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 1 | 0 | .4615 | . | .5556 | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 68 | 68 | 69 | 66 | 69 | | | | | |
| C-CELL ADENOMA | 4 | 1 | 1 | 0 | 4 | .2153 | .5599 | 1 | .9688 | .9752 |
| C-CELL CARCINOMA | 1 | 1 | 3 | 0 | 0 | .9489 | 1 | 1 | .2994 | .7690 |
| C-Cell Adenoma/Carcinoma | 5 | 2 | 4 | 0 | 4 | .5367 | .6812 | 1 | .7464 | .9511 |
| FOLLICULAR CELL ADENOMA | 0 | 1 | 1 | 0 | 1 | .2783 | .4568 | . | .4943 | .5217 |
| FOLLICULAR CELL CARCINOMA | 1 | 0 | 0 | 2 | 1 | .3200 | .7080 | .4824 | 1 | 1 |
| Foll. Cell Adenoma/Carcinoma | 1 | 1 | 1 | 2 | 2 | .2147 | .4345 | .4824 | .7471 | .7740 |
| UTERUS W/ CERVIX | | | | | | | | | | |
| # Evaluated | 69 | 69 | 69 | 69 | 70 | | | | | |
| ENDOMETRIAL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2189 | .4512 | . | . | . |
| ENDOMETRIAL STROMAL POLYP | 4 | 2 | 6 | 2 | 1 | .9530 | .9528 | .8934 | .3268 | .9119 |
| Endo. Carc./Stromal Polyp | 4 | 2 | 6 | 2 | 2 | .8545 | .8408 | .8934 | .3268 | .9119 |
| LEIOMYOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| MALIGNANT SCHWANNOMA | 2 | 1 | 0 | 0 | 2 | .2363 | .6270 | 1 | 1 | .8903 |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 0 | 0 | 0 | 1 | 0 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |



Reference ID: 3063799

## Table A.3.4 Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADIPOSE TISSUE | | | | | | | | | | |
| # Evaluated | 4 | 2 | 2 | 3 | 2 | | | | | |
| LIPOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .3333 |
| ADRENALS | | | | | | | | | | |
| # Evaluated | 62 | 65 | 62 | 65 | 64 | | | | | |
| CORTEX: ADENOMA | 2 | 2 | 5 | 2 | 5 | .2061 | .2047 | .7020 | .1832 | .7518 |
| Alimemtary Canal | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| Adenoma | 0 | 1 | 2 | 0 | 1 | .4243 | .4872 | . | .2468 | .5294 |
| DISTAL FEMUR | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| OSTEOMA | 0 | 0 | 0 | 1 | 0 | .4968 | . | .5000 | . | . |
| EYES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| ADENOMA, SEBACEOUS | 0 | 0 | 0 | 1 | 1 | .1823 | .4872 | .5062 | . | . |
| HARDERIAN GL | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 64 | | | | | |
| ADENOMA | 10 | 5 | 9 | 6 | 6 | .8077 | .8693 | .9097 | .6561 | .9682 |
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| TUBULAR ADENOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5294 |
| LIVER | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEPATOCELLULAR ADENOMA | 5 | 8 | 11 | 7 | 6 | .6319 | .4638 | .3956 | .0990 | .3549 |
| HEPATOCELLULAR CARCINOMA | 17 | 15 | 17 | 15 | 18 | .3623 | .4649 | .7709 | .5531 | .8489 |
| Hepato. Adenoma/Carcinoma | 19 | 22 | 25 | 21 | 21 | .5239 | .4153 | .5269 | .1697 | .5172 |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0 | .7468 | . | . | .5000 | . |
| LUNGS | | | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | 65 | | | | | |
| BRONCHIOLAR/ALVEOLAR ADENOMA/CY | 6 | 9 | 5 | 6 | 4 | .7014 | .8121 | .6044 | .7113 | .3731 |
| BRONCHIOLAR/ALVEOLAR CARCINOMA | 6 | 11 | 6 | 6 | 3 | .8589 | .9039 | .6220 | .6042 | .2219 |
| Bronch. Alv. Adenoma/Carcinoma | 11 | 18 | 10 | 11 | 7 | .8444 | .8886 | .5978 | .6700 | .1978 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| GRANULOCYTIC LEUKEMIA | 0 | 0 | 1 | 1 | 1 | .2864 | .4872 | .5062 | .4937 | . |
| HISTIOCYTIC SARCOMA | 1 | 1 | 1 | 1 | 0 | .8218 | 1 | .7469 | .7405 | .7756 |
| MALIGNANT LYMPHOMA | 7 | 9 | 14 | 7 | 12 | .2419 | .1493 | .6144 | .0740 | .4694 |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 62 | 65 | 63 | 65 | 65 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 63 | 64 | 62 | 64 | 65 | | | | | |
| PARS DISTALIS-ADENOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5301 |
| RECTUM/LOW COLON | | | | | | | | | | |
| # Evaluated | 61 | 65 | 65 | 64 | 62 | | | | | |
| ADENOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5422 |
| SKIN | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| FIBROMA | 0 | 0 | 1 | 0 | 0 | .7452 | . | . | .4937 | . |
| FIBROSARCOMA | 2 | 1 | 1 | 0 | 0 | .9835 | 1 | 1 | .8703 | .8958 |
| SEBACEOUS CELL ADENOMA | 0 | 0 | 1 | 0 | 0 | .7452 | . | . | .4937 | . |
| STOMACH | | | | | | | | | | |
| # Evaluated | 64 | 64 | 65 | 65 | 65 | | | | | |
| GLANDULAR MUCOSA: ADENOMA | 0 | 0 | 2 | 0 | 1 | .4243 | .4872 | . | .2468 | . |



Reference ID: 3063799

## Table A.3.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEMANGIOMA | 0 | 0 | 0 | 2 | 0 | .4904 | . | .2468 | . | . |
| HEMANGIOSARCOMA | 3 | 3 | 0 | 2 | 2 | .4236 | .7960 | .8127 | 1 | .7153 |
| Hemangioma/Hemangiosarcoma | 3 | 3 | 0 | 4 | 2 | .4457 | .7960 | .4860 | 1 | .7153 |
| MESOTHELIOMA | 0 | 0 | 0 | 1 | 1 | .1823 | .4872 | .5062 | . | . |
| TESTES | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN INTERSTITIAL CELL TUMOR | 1 | 1 | 0 | 0 | 3 | .0442 | .2883 | 1 | 1 | .7815 |
| THYROID | | | | | | | | | | |
| # Evaluated | 62 | 60 | 62 | 64 | 62 | | | | | |
| FOLLICULAR CELL ADENOMA | 0 | 0 | 0 | 0 | 1 | .2436 | .4872 | . | . | . |
| ZYMBAL'S GLAND | | | | | | | | | | |
| # Evaluated | 1 | 0 | 0 | 0 | 0 | | | | | |
| CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | . | . | . | . |

## Table A.3.5 Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| ADRENALS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 64 | | | | | |
| CORTEX: ADENOMA | 1 | 1 | 1 | 0 | 1 | .5176 | .7305 | 1 | .7363 | .7675 |
| MEDULLA: MALIGNANT PHEOCHROMOCY | 0 | 0 | 0 | 1 | 0 | .4890 | . | .4839 | . | . |
| Alimemtary Canal | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| Adenoma/Carcinoma | 0 | 0 | 0 | 1 | 1 | .1837 | .4894 | .4783 | . | . |
| BICEP FEMORIS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| SCHWANNOMA | 0 | 0 | 0 | 1 | 0 | .4918 | . | .4839 | . | . |
| BRAIN | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN MENINGIOMA | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| OLIGODENDROGLIOMA | 0 | 0 | 0 | 1 | 0 | .4890 | . | .4783 | . | . |
| DISTAL FEMUR | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 1 | 0 | .4918 | . | .4839 | . | . |
| GALLBLADDER | | | | | | | | | | |
| # Evaluated | 51 | 59 | 54 | 56 | 53 | | | | | |
| PAPILLOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5412 |
| HARDERIAN GL | | | | | | | | | | |
| # Evaluated | 65 | 65 | 64 | 65 | 65 | | | | | |
| ADENOMA | 5 | 5 | 9 | 9 | 10 | .1627 | .1208 | .1814 | .1698 | .6679 |
| CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| KIDNEYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| TUBULAR CARCINOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5102 |



Reference ID: 3063799

**Table A.3.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| LIVER | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| CHOLANGIOCARCINOMA | 0 | 0 | 0 | 1 | 0 | .4890 | . | .4783 | . | . |
| HEPATOCELLULAR ADENOMA | 0 | 0 | 2 | 0 | 1 | .4241 | .4839 | . | .2368 | . |
| HEPATOCELLULAR CARCINOMA | 0 | 1 | 1 | 2 | 1 | .3127 | .4839 | .2260 | .4839 | .5152 |
| Hepato. Adenoma/Carcinoma | 0 | 1 | 3 | 2 | 2 | .3023 | .2314 | .2260 | .1132 | .5152 |
| OSTEOSARCOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5102 |
| LUNGS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BRONCHIOLAR/ALVEOLAR ADENOMA/CY | 5 | 6 | 4 | 2 | 3 | .7265 | .8447 | .9340 | .7125 | .5423 |
| BRONCHIOLAR/ALVEOLAR CARCINOMA | 3 | 3 | 0 | 1 | 1 | .7037 | .9305 | .9274 | 1 | .6801 |
| Bronch. Alv. Adenoma/Carcinoma | 7 | 9 | 4 | 3 | 4 | .7151 | .8724 | .9396 | .8643 | .4432 |
| LYMPH/RETIC SYS | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| GRANULOCYTIC LEUKEMIA | 1 | 0 | 0 | 0 | 1 | .4406 | .7419 | 1 | 1 | 1 |
| HISTIOCYTIC SARCOMA | 2 | 7 | 4 | 3 | 4 | .2907 | .3286 | .4796 | .3286 | .1003 |
| MALIGNANT LYMPHOMA | 14 | 7 | 10 | 17 | 11 | .5782 | .7177 | .2442 | .8136 | .9693 |
| MAMMARY PROTOCOL | | | | | | | | | | |
| # Evaluated | 56 | 59 | 60 | 61 | 60 | | | | | |
| ADENOCARCINOMA | 0 | 2 | 1 | 0 | 1 | .3129 | .5000 | . | .5000 | .2824 |
| MESENTERIC LN | | | | | | | | | | |
| # Evaluated | 60 | 60 | 54 | 59 | 61 | | | | | |
| OSTEOSARCOMA | 0 | 0 | 0 | 0 | 1 | .2647 | .5000 | . | . | . |
| OVARIES | | | | | | | | | | |
| # Evaluated | 64 | 65 | 64 | 65 | 65 | | | | | |
| BENIGN GRANULOSA CELL TUMOR | 2 | 1 | 1 | 1 | 0 | .9223 | 1 | .8665 | .8709 | .8900 |
| CYSTADENOMA/ADENOMA, OVARY OR O | 0 | 0 | 1 | 3 | 0 | .6978 | . | .1130 | .4946 | . |
| LUTEOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| MALIGNANT GRANULOSA CELL TUMOR | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| SERTOLI CELL TUMOR | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| PANCREAS | | | | | | | | | | |
| # Evaluated | 65 | 64 | 64 | 64 | 64 | | | | | |
| ISLET CELL ADENOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| PITUITARY | | | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 63 | 64 | | | | | |
| PARS DISTALIS-ADENOMA | 3 | 0 | 2 | 0 | 1 | .8323 | .9334 | 1 | .7986 | 1 |
| PSOAS MUSCLE | | | | | | | | | | |
| # Evaluated | 0 | 1 | 0 | 1 | 0 | | | | | |
| FIBROSARCOMA | 0 | 0 | 0 | 1 | 0 | 1 | . | . | . | . |
| SKIN | | | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | 65 | | | | | |
| FIBROSARCOMA | 1 | 2 | 0 | 0 | 1 | .4344 | .7363 | 1 | 1 | .5078 |
| MAST CELL TUMOR | 0 | 0 | 0 | 0 | 1 | .2514 | .4894 | . | . | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2473 | .4839 | . | . | . |
| SQUAMOUS CELL PAPILLOMA | 0 | 0 | 0 | 0 | 1 | .2473 | .4839 | . | . | . |
| STOMACH | | | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 64 | 65 | | | | | |
| FORESTOMACH: SQUAMOUS CELL CARC | 0 | 0 | 0 | 1 | 0 | .4890 | . | .4783 | . | . |
| GLANDULAR MUCOSA: ADENOMA | 0 | 0 | 0 | 0 | 1 | .2514 | .4894 | . | . | . |



Reference ID: 3063799

**Table A.3.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice**

| Organ Tumor | Incidence Veh1 w/s | Veh2 wo/s | Low | Med | Hi | Significance Levels trend | High vs V1 | Med vs V1 | Low vs V1 | Veh2 vs V1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| HEMANGIOMA | 2 | 2 | 4 | 6 | 4 | .3485 | .3286 | .1203 | .3184 | .7140 |
| HEMANGIOSARCOMA | 4 | 5 | 2 | 2 | 0 | .9786 | 1 | .8774 | .8830 | .5257 |
| Hemangioma/Hemangiosarcoma | 6 | 6 | 6 | 8 | 4 | .7715 | .8240 | .3545 | .5904 | .6617 |
| TAIL | | | | | | | | | | |
| # Evaluated | 5 | 0 | 0 | 0 | 1 | | | | | |
| CHORDOMA | 0 | 0 | 0 | 0 | 1 | .2500 | .2500 | . | . | . |
| THYROID | | | | | | | | | | |
| # Evaluated | 65 | 62 | 62 | 64 | 63 | | | | | |
| C-CELL ADENOMA | 0 | 0 | 0 | 0 | 1 | .2458 | .4783 | . | . | . |
| FOLLICULAR CELL ADENOMA | 0 | 1 | 0 | 0 | 0 | . | . | . | . | .5052 |
| UTERUS W/ CERVIX | | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | 65 | | | | | |
| BENIGN GRANULAR CELL TUMOR | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| ENDOMETRIAL CARCINOMA | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| ENDOMETRIAL STROMAL POLYP | 4 | 7 | 6 | 7 | 6 | .3570 | .3565 | .2495 | .3428 | .3230 |
| ENDOMETRIAL STROMAL SARCOMA | 2 | 0 | 1 | 1 | 0 | .9201 | 1 | .8623 | .8667 | 1 |
| Endo. Stromal Adenoma/Sarcoma | 6 | 7 | 7 | 8 | 6 | .5615 | .5904 | .3545 | .4505 | .5610 |
| LEIOMYOMA | 0 | 3 | 3 | 1 | 1 | .5303 | .4839 | .4783 | .1132 | .1328 |
| LEIOMYOSARCOMA | 4 | 4 | 1 | 3 | 0 | .9584 | 1 | .7457 | .9653 | .6648 |
| Leiomyoma/Leiomysarcoma | 4 | 7 | 4 | 4 | 1 | .9217 | .9653 | .5938 | .6066 | .2860 |
| VAGINA | | | | | | | | | | |
| # Evaluated | 64 | 64 | 62 | 65 | 64 | | | | | |
| ADENOMA | 0 | 0 | 0 | 1 | 1 | .1851 | .4891 | .4891 | . | . |
| LEIOMYOMA | 0 | 0 | 0 | 0 | 1 | .2500 | .4891 | . | . | . |
| SQUAMOUS CELL CARCINOMA | 0 | 0 | 0 | 0 | 1 | .2500 | .4891 | . | . | . |



Reference ID: 3063799

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Reference ID: 3063799

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/s/

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STEVEN F THOMSON
12/23/2011
Statistical carcinogenicity Review

KARL K LIN
12/23/2011
Concur with review

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 203188** **Applicant: Vertex Pharmaceuticals** **Stamp Date: 10-18-2011**

**Drug Name: Kalydeco (Ivacaftor)** **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc. | x | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | x | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | x | | | |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | x | | | |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. NONE

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | x | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | x | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | x | |
| Appropriate references for novel statistical methodology (if present) are included. | | | x | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | x | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | x | | | |

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| | |
|---|---|
| David Hoberman | 11-18-2011 |
| Reviewing Statistician | Date |
| Joan Buenconsejo | 11-18-2011 |
| Supervisor/Team Leader | Date |

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

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DAVID HOBERMAN
12/02/2011

JOAN K BUENCONSEJO
12/02/2011
I concur with Dr. Hoberman's checklist